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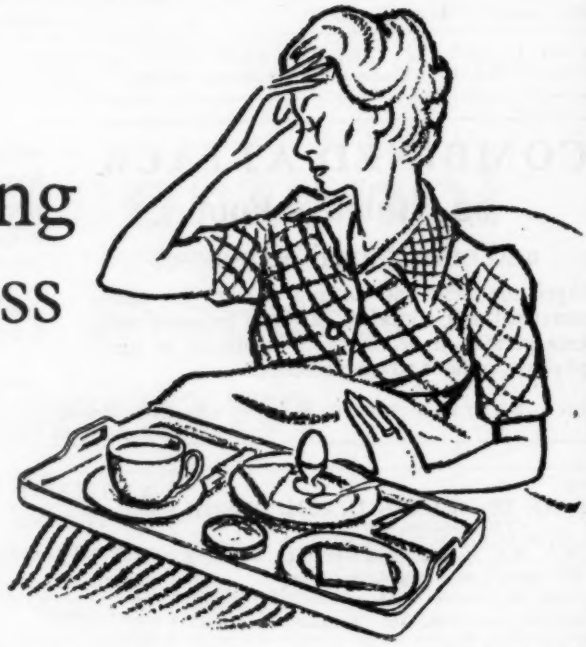

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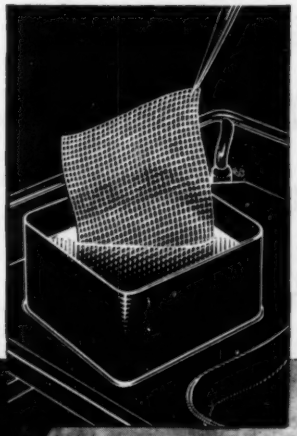

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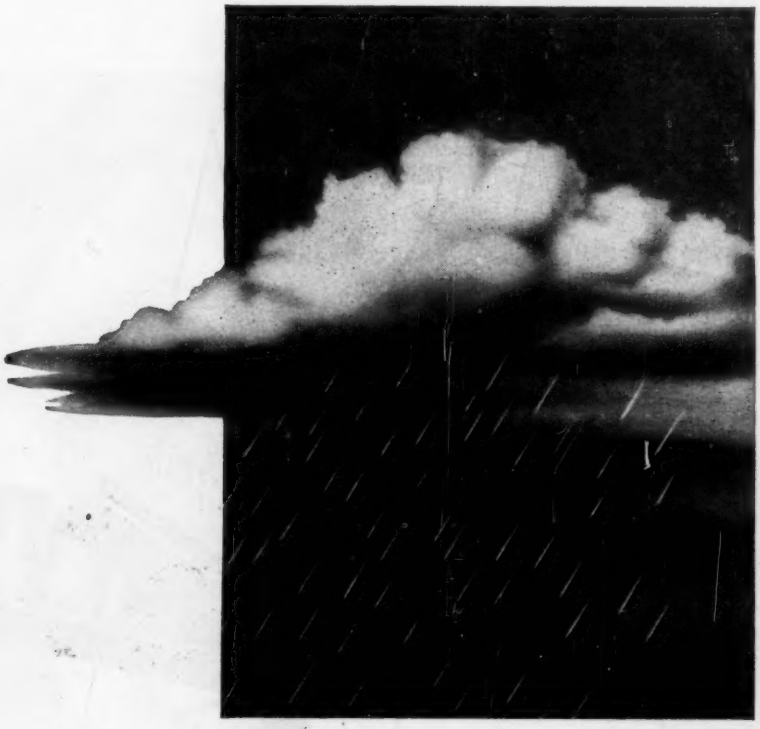

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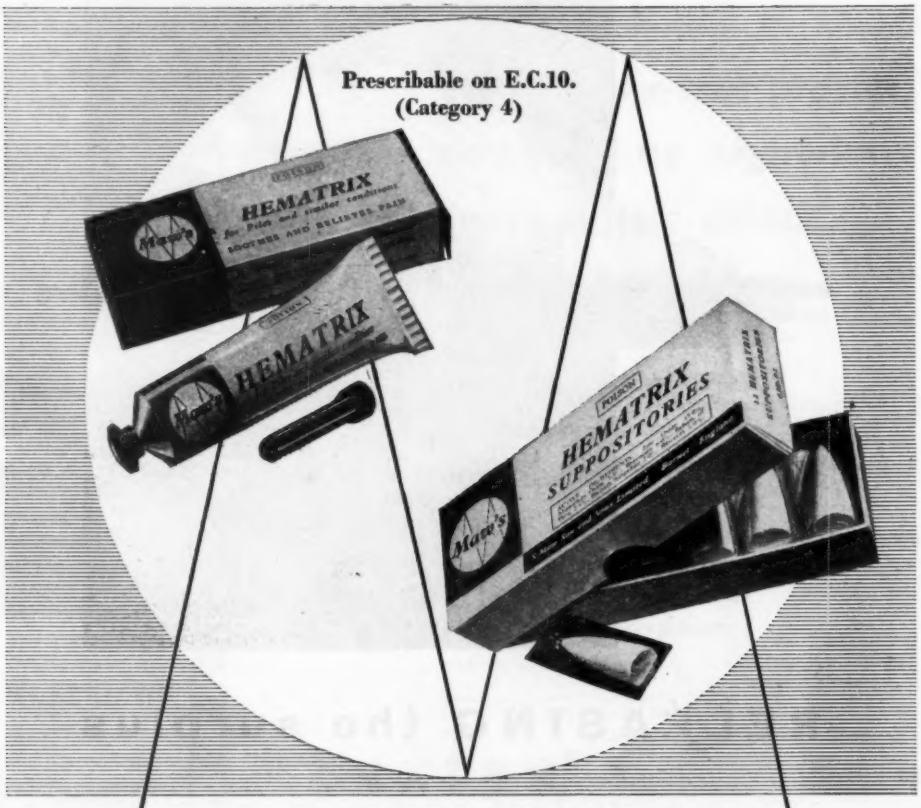

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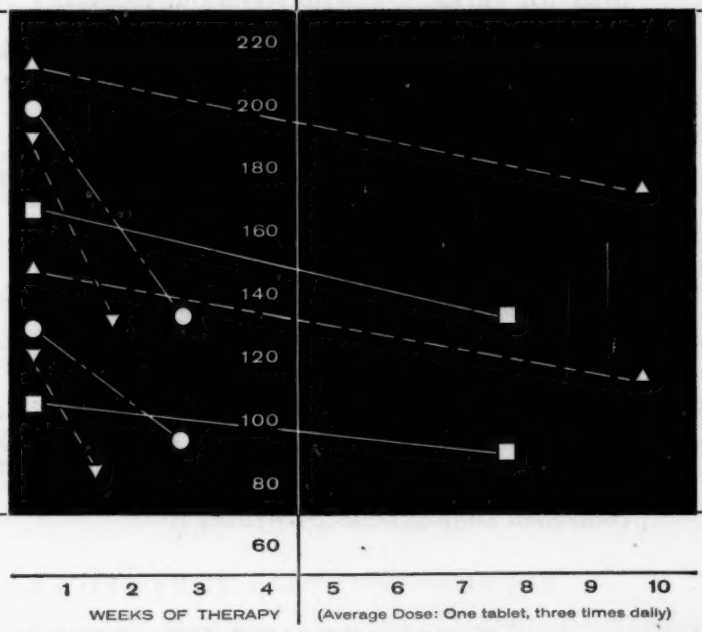

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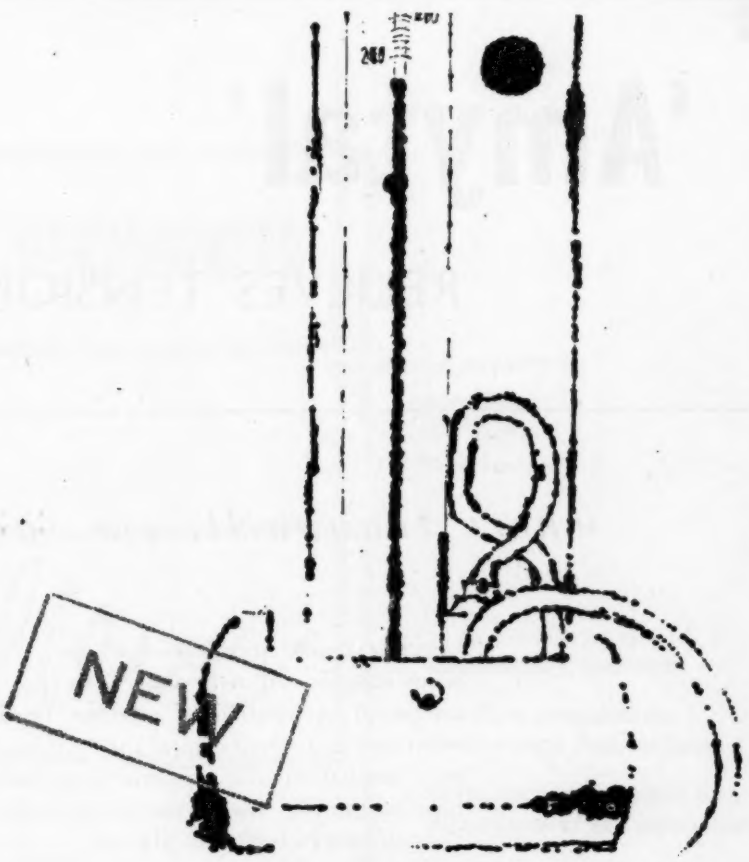

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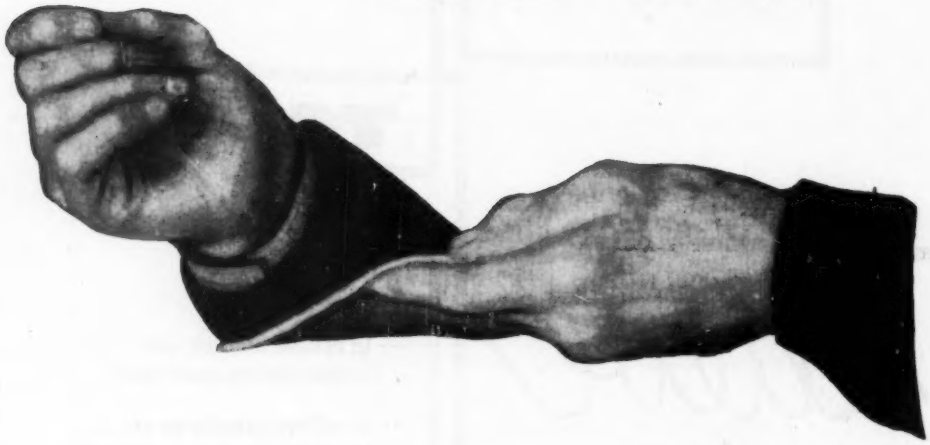

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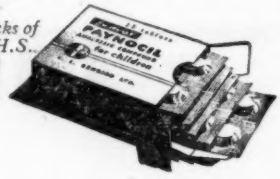

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SOME PRINCIPLES OF HOMŒOSTASIS*

DOUGLAS HUBBLE
M.D. Lond., F.R.C.P.
PHYSICIAN, DERBYSHIRE ROYAL INFIRMARY AND THE DERBYSHIRE CHILDREN'S HOSPITAL

THE word "homœostasis" was invented by the fine and thoughtful American physiologist, Walter B. Cannon (1932). We must agree then that "homœostasis" has some pride of parentage and, in view of its considerable usage today, it has also some expectation of immortality. Fortunately its meaning is well understood, for if we break the word down into its component parts—"of a like or equal stagnation"—we have little enough help towards a definition of it. "Homœostasis" denotes the constancy of the body's internal environment and it crystallises the concept of Claude Bernard, the great French physiologist, who wrote that "the fixity of the internal environment is the condition of the free life." You will remark the antithesis between "fixity" and "freedom," a suggestion that it is because of this inner constancy that man's life is free. Now, scientific aphorisms should in general be suspect, and we must take a good look at this one. It might be argued, for example, that the constancy of man's temperature gave him freedom from the need to fall asleep with the tortoise in the winter, or freedom from the impulse to fly to North Africa with the swallow; but man is bound by other imperious impulses from which the animals and birds are free. Joseph Barcroft examined Bernard's aphorism in the first three chapters of his book *Features in the Architecture of Physiological Function* and concluded that it could be commendably interpreted only as meaning that this constancy of internal environment had allowed the development of man's intellect and therefore of man's ability to comprehend both himself and his environment; and of man's intellectual ascendancy, the "free life," said Barcroft, "was no inapt description."

While some physiologists, then, have concluded that man's life is "free" (though not fully justifying this as a physiological conclusion), other physiologists have suggested that man's body is "wise." Starling, the distinguished circulatory physiologist, took as the text for his Harveian oration to the Royal College of Physicians of London on St. Luke's Day, 1923, "Who hath put wisdom in the inward parts? or who hath given understanding to the heart?" Our generation is more likely to join with St. Francis in deriding, however gently, the body as an ass, than with Starling and Cannon (who, following Starling's example, entitled his best-known book *The Wisdom of the Body*) in finding wisdom in the nodal action of the heart or in renal tubular function. The most we might allow of wisdom to the body can be expressed by an amendment of Pascal's famous epigram that "the (*anatomical*) heart has its reasons which the reason knows not." We must seek to avoid on the one hand the near-anthropomorphic heresy of Starling, and on the other the self-denigrating taunt of St. Francis. Our approach to the complexities of body function is the middle way of seeking that comprehension which Barcroft saw as an important consequence of man's intellectual ascendancy.

Barcroft decided not to include the endocrine system in his discussion of the factors concerned in maintaining the body's internal constancy. This allows me to use endocrine and metabolic homœostasis in illustration of the results of homœostatic action when the body is confronted by disease; and this is the more fortunate since I am not competent either to comment on, or to extend, Barcroft's admirable work, which is occupied mainly with the blood and with respiration, with the circulation, and with the nervous system.

Homœostasis and Evolutionary Adaptation

Homœostasis comprises a great variety of mechanisms which man and animals have developed in the ages of evolutionary experience. *How* these mechanisms maintain body function in a state of equilibrium is the object of continuous inquiry: *why* the value of the plasma constants has been fixed at certain levels must await more knowledge of cellular chemistry. Why, for example, are 3 μg. of thyroxine, 60 mg. of sugar, and 8 mg. of calcium per 100 ml. of plasma too little, and 9 μg. of thyroxine, 130 mg. of fasting sugar, and 13 mg. of calcium per 100 ml. of plasma too much? The range of normal values, you will see, is often remarkably narrow:

> "Oh, the little more, and how much it is!
> And the little less, and what worlds away!"

The range of normality in the lower vertebrates, for some at least of these constants, is greater than in man; for example, the maximum blood-sugar in chickens varies between 200 and 350 mg. per 100 ml. of blood. When we recall that glucose provides the main foodstuff for the cerebral cells, we can see a reason for the range of blood-sugar being more narrow in man than in chickens, but this gives us no clue as to why the top level in man eventually became fixed at 180 mg. per 100 ml. of plasma.

We assume that nervous tissue finds it difficult to extract sugar from the blood if its level falls below 50 mg. per 100 ml., but we should very much like to know whether any harm comes directly to any cells in the body when the blood-sugar is consistently above, say, 250 mg. per 100 ml., or whether the evil that may result is the effect solely of the body's homœostatic reactions to hyperglycæmia.

The *first principle for us to consider, then, is that the homœostatic mechanisms were established for survival in, and for adaptation to, an unkind world.* Since they are evolutionary mechanisms, they were designed to assist man's elementary struggles, against cold, hunger, thirst, and injury, and they are not concerned with assisting him in his struggle against disease. We must expect, therefore, that homœostatic mechanisms will assist us in our therapeutic attempts only when disease mimics one of these primitive situations. The ways in which the body counteracts hypoglycæmia are, as we shall see, many and varied, because hunger was a common primitive emergency; on the other hand, to hyperglycæmia, which was not a primitive biological situation and which arises only when insulin fails or is overcome, the body has the one unsatisfactory reply of excreting the excess of sugar through the kidney. We find, too, that when our therapeutic methods oppose exaggerated homœostatic mechanisms, as in the surgical and medical treatment of essential hypertension, the autonomic nervous system seeks to correct and reverse our therapies.

The anæsthetists have in the past few years used one of the body's ancient and forgotten homœostatic reactions—that against cold—to produce a hibernating poikilothermic animal, which, by slowing of the circulation, allows the cardiac surgeon, more time for his plastic manœuvres.

It is a common observation that the course of evolution has left our bodies with structures, such as the appendix, which are a hazard to the survival of the individual. The comment has also been made that if our fishy forebears had foreseen that their descendants would one day forsake the sea and take to the hills they might have used a handy halogen, other than iodine, in the synthesis of the thyroid hormone (Hubble 1956). Our bodies are

* The Burns lecture delivered to the Royal Faculty of Physicians and Surgeons, Glasgow, on Jan. 30, 1957.

handicapped, not only by primitive structures, but also by the need to elaborate chemical compounds, such as the iodinated proteins, more appropriate to an earlier environment.

Primitive functions unsuitable for our present environment have also persisted, and this, too, affects homœostasis. Gamble (1954) has, as you know, suggested that the chemical skeleton of sea-water is clearly visible in the body's extracellular fluid, and Homer Smith (1932) has shown us that man is actually endowed with a "fresh-water" kidney. The glomerulo-tubular kidney first appeared in fresh-water vertebrate fishes in which, swimming around in a hypotonic fluid, it was important that essential substances should be conserved in the presence of a very large removal of water. This was excellently met by the device of filtration in the kidney followed by reabsorption from a large surface provided by a long tube. When fish took to salt water they were faced with the different problem of a hypertonic environment so that their salt intake was in relative excess to their water intake. They had the need, therefore, to raise their plasma osmotic level in order to secrete a hypertonic urine, and this the cartilaginous fishes did by adding the physiologically inert substance urea to the plasma. Filtration by the glomerulus allowed no advantage, so the glomerulus disappeared partly or completely from salt-water fish. Man is, however, left with a "fresh-water" kidney in his terrestrial environment. A kidney designed to get rid of water now has the task of conserving water; by the addition of the loop of Henle the human kidney is able to excrete a urine which is greatly hypertonic to plasma (fig. 1). To do this the kidneys have to reabsorb each day 180 litres of water and more than a kilogramme of salt. Gamble remarks that this method, although fortuitous, works with a "beautiful accuracy." Pædiatricians have, however, been taught by McCance and Young (1941) and have had the lesson reinforced by hard experience, that the infant kidney does not achieve its essential part in the homœostasis of water and salt for a year or so after the infant has escaped from its watery existence. The crucial rôle of the loop of Henle in homœostasis provides us with an adequate explanation for this delay and is, further, an illustration of the way in which the consequences of adaptation in evolution may remain as hazards to homœostasis.

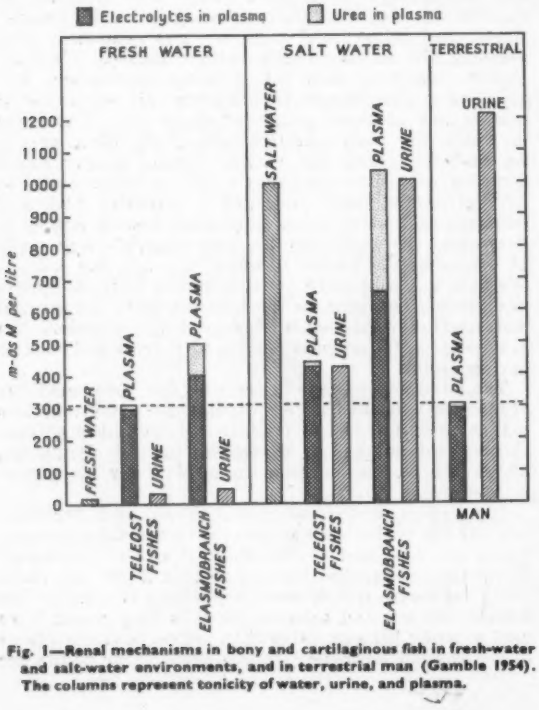


Fig. 1—Renal mechanisms in bony and cartilaginous fish in fresh-water and salt-water environments, and in terrestrial man (Gamble 1954). The columns represent tonicity of water, urine, and plasma.

Homœostatic mechanisms have been shown, then, to oppose therapeutic procedures, as in hypertension; to assist them, as in operations conducted under hypothermia; and, in the late acquisition by the infant kidney of control of salt and water homœostasis, to make necessary great caution in treatment. We shall be able to trace further the hand of evolution in homœostasis as we now consider the methods used by the body for the maintenance of the blood-sugar, for the provision of cellular protein, and for the regulation of the hormones in the endocrine system.

Maintenance of the Blood-sugar

No substance has a greater importance in chemical homœostasis than sugar, for the reason that the brain immediately fails in its function when deprived of this essential nutrient. Most of the substances which are important in the body economy appear to be controlled by mechanisms which regulate both their absorption and their excretion. In the case of glucose, the metabolic processes in the intestinal wall which prevent the absorption of an excess of it are probably similar to those which also prevent the transport of too much of it across the renal tubule (Long 1952). In both sites the rate of absorption can be altered by endocrine action and is adjusted to the level of glucose, in the blood in the case of absorption, and, in the case of excretion, to the level in the glomerular filtrate. Both these methods obviously can, by ensuring maximal absorption in the intestine and complete absorption in the renal tubule, play a useful part in the homœostatic prevention of *hypoglycæmia*, but neither is of use in the body's handling of the hypoglycæmic situation when it is urgent. The defences of the body against hypoglycæmia are, in the absence of excessive insulin action whether exogenous or endogenous, very effective. They are designed to mobilise glucose from glycogen, to form glucose from protein (gluconeogenesis), and to diminish the utilisation of glucose by the tissues, with which appears to be associated a depression of insulin-formation. The first method, the conversion of glycogen in the liver and the muscles, is obviously a method of emergency; if this fails to elevate the blood-sugar to normal levels, then the long-range methods are called upon. We may assume that all these homœostatic methods were elaborated to combat starvation, but all of them can be seen exerting an influence in disease and on our treatment of it.

Adrenaline is the hormone which accelerates the breakdown of glycogen both in the liver and in the muscles, and this is the *rapid* reaction to hypoglycæmia. I use the word "rapid" rather than "immediate" because Bearn, Billing, and Sherlock (1952) showed, by the technique of catheterisation of the hepatic veins, a rise in the level of blood-sugar therein which is too quick to be due to adrenaline release. It is probable that this is associated with a local hepatic reaction to hypoglycæmia, reinforced as it is quite quickly by adrenaline, and possibly assisted also by the liberation of glucagon, which is a hyperglycæmic-glycogenolytic factor, produced, it may be, by the α-cells of the pancreas.

Here then are two, and possibly three, mechanisms which break down hepatic glycogen to glucose. Let us call these mechanisms "the immediate" and "the delayed immediate," to emphasise the time factor in these responses.

The discharge of adrenaline into the blood-stream initiates the release of corticotrophin (A.C.T.H.) from the pituitary. The increased secretion of corticotrophin

stimulates the adrenal cortex to the production of hydrocortisone, and this—as every medical counterpart of Macaulay's schoolboy knows today—brings about the conversion of protein to glucose. It has also been shown in animals that the adrenocortical hormones depress the utilisation of carbohydrate by the tissues. The growth hormone, at any rate in animals, will also depress the utilisation of carbohydrate by the tissues.

Here, then, are four mechanisms by which the body responds to the hypoglycæmic situation, and five hormones (adrenaline, corticotrophin, hydrocortisone,

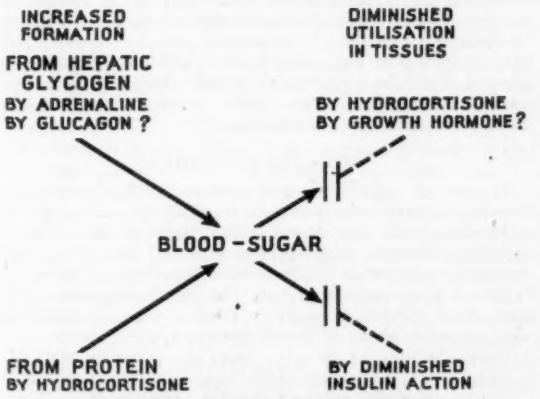


Fig. 2—Mechanisms controlling hypoglycæmia.

insulin, and the growth hormone) with possibly a sixth (glucagon) which are concerned in this homœostasis of blood-sugar (fig. 2).

We may, therefore, conclude as a second principle that *where the consequences of homœostasis are vital to survival, the body does not rely on a single mechanism but has at its command several mechanisms all with a single objective*—in this case the maintenance of the blood-sugar to ensure the proper function of the central nervous system.

As we consider the reaction to hypoglycæmia in disease, we see that of these homœostatic mechanisms, the two associated with glycogenolysis are emergency measures, while the two associated with glyconeogenesis and diminished insulin action are also used to meet a chronic deficiency of carbohydrate. *The third principle, then, is that where there are multiple mechanisms employed in homœostasis, some are designed for an emergency, and others are used to meet a situation which may be indefinitely prolonged.*

Let us now look at some of the disorders of blood-sugar control in man, remembering again that homœostasis was not designed to meet pathological situations. Where an excessive amount of insulin is being formed, as in an insulin adenoma, the body's homœostatic mechanisms are severely taxed and frequently fail. The situation is particularly dangerous in infants and children, for in them protein is required for growth and is not available for gluconeogenesis, and the most valuable of the long-acting mechanisms is removed. Chronic hypoglycæmic situations arise also in *glycogen-storage disease*, where hepatic glycogen is not available for discharge into the blood as glucose. Bridge and Holt (1945) showed, many years ago in their classic paper, that this problem can be solved, at least partially, by giving enough protein for growth and an extra allowance especially at night, for gluconeogenesis. These considerations also explain van Creveld's (1952) later observation that children with glycogen-storage disease may, in adult life, exercise their reproductive functions, though their hepatic defect remains. As the insistent need of protein for growth abates, it becomes available for other purposes; there is enough for gluconeogenesis and enough also for the development of sexual function. We may note in passing that the same requirements of protein for growth in young children make necessary the use of fat for energy, with the increased liability to ketosis which this entails. The provision of extra protein for ketotic children is more rational than the administration of glucose.

In diabetes, though there is hyperglycæmia, the tissues, in the absence of insulin, are in a hypoglycic state, and the consequent breakdown of protein by hydrocortisone for gluconeogenesis adds glucose to blood already overcharged with it. Homœostasis of blood-sugar was designed not to meet an insulin deficiency, but to counteract hypoglycæmia. I have already referred to the multiple methods on which the body relies for the maintenance of the blood-sugar. Note again how different is the situation for opposing hyperglycæmia. Here there are only two responses—an increased output of insulin and the excretion of sugar in the urine. When insulin fails or its action is resisted, glycosuria is the only response available. It certainly appears that the evils which result from hyperglycæmia are related, not directly to the high level of the blood-sugar, but, firstly, to the increased demands on insulin production; secondly, to the results of glycosuria; and thirdly, to the homœostatic consequences when glucose cannot be used by the tissues. The new hypoglycæmic agents, such as carbutamide and tolbutamide, will obviously remove the first two effects of hyperglycæmia, though I do not think they make carbohydrate more available to the tissues and, therefore, they will not prevent the important homœostatic consequences that follow from this cause. When sufficient carbohydrate is not available for energy, the body necessarily moves over to fat katabolism, with consequences for the diabetic well known to all of us. Talbot et al. (1952) have pointed out that dehydration, carbohydrate starvation, ketosis, and acidosis in diabetes excite the pituitary-adrenocortical alarm reaction. This exaggerates many of the noxious features of diabetic ketosis—it may account for the loss of potassium in excess of nitrogen from the cells of the body, for insulin resistance, and for an enhancement of ketosis by assisting in the mobilising of fat from the depots. The last state of the diabetic man is thereby made worse than the first. Who, indeed, "hath put wisdom in the inmost parts?"

Homœostatic mechanisms, then, we may conclude, will ameliorate pathological hypoglycæmia, but they give us no help in dealing with insulin-deficient hyperglycæmia, and in diabetic ketosis they worsen a situation already dangerous.

The Homœostasis of Protein Metabolism

If we knew that the constancy of glucose in the plasma facilitated satisfaction of the changing requirement of the cells for carbohydrate, and if we knew that the constancy of the plasma amino-acids made possible the provision of protein for cellular growth, then we could see here another illustration of, and a further justification for, Bernard's aphorism—an antithesis between the "fixity" of the plasma nutrients and the "free life" of the cells. Our present knowledge of the passage of substances across cell-membranes does not yet justify this statement; so we can only pay attention to this remarkable contrast.

We must widen our concept of a fixed internal metabolic environment to include the pattern of cellular metabolism. Appetite and hormonal influences gear the provision of nutrients for the cells in excess of those needed for energy and repair, and we can see in consequence an overall metabolic pattern which may lead to an excess of fat being deposited in the depots or to the growth of young animals. Equilibrium is achieved,

in the one case, by obesity, and in the other by an excess of protein anabolism over katabolism, which causes growth.

Growth may be regarded as the result of a competition for protein which is won by the anabolising hormones. The hormones which effect protein anabolism are the growth hormone, supported by insulin and thyroxine, and the androgens, which initiate the growth-spurt at puberty. The hormone which effects protein katabolism is hydrocortisone, and it does so, as we have seen, by gluconeogenesis.

In infancy and childhood, the growth hormone, with its supporters thyroxine and insulin, are dominant; at puberty the androgens from the adrenal in both sexes, and from the testis in the male, reinforce this dominance and there is a growth-spurt. In adult life a balance is struck between the anabolisers and the katabolisers, and bone metabolism is active but homœostatic until, after the menopause in women (who lack the protein anaboliser provided by the testis in men), the bones yield up their protein and pathological osteoporosis is common. I have expressed these facts by four formulas which illustrate these hormonal balances in life's various stages:

THE FOUR SKELETAL AGES OF WOMAN

$G + T + I \quad > H$: Growth in infancy and childhood.
$G + T + I + A > H$: Growth in adolescence.
$g + T + I + A \equiv H$: Arrest of growth in adult life.
$g + T + I + a < H$: Post-menopausal osteoporosis.

Where G and g are the growth hormones, T thyroid, I insulin A and a androgens, and H hydrocortisone.

Let us see how this protein balance of retention and breakdown is affected by disease, and let us use these pathological processes to test the validity of the formula.

When disease in children results in an excess of the protein anabolisers, growth increases. This is seen in the rapid growth of children who are developing thyrotoxicosis; in the increased growth of children before diabetes overtakes them (Priscilla White's observation, and we guess, but are not yet certain, that this relates to an excess of growth hormone); and in those hyperplasias of the adrenal cortex in children in which an excess of adrenal androgens is secreted (together with a diminished secretion of hydrocortisone on the right-hand side of my formula).

When hydrocortisone is used in treatment of children, growth may be impeded, but not epiphyseal development (Ansell and Bywaters 1956), proving that the hydrocortisone has not interfered with the production of the growth hormone but has overthrown it in the competition for protein. In a boy of mine, aged $8^1/_2$, with Cushing's syndrome due to adrenocortical hyperplasia, growth had stopped for two years (Hubble and Illingworth 1957).

When the protein anabolisers are scarce, as in hypopituitarism, growth is impeded. If in pituitary dwarfs with a presumed absence of growth hormone, not due to organic disease, hydrocortisone production were to proceed at its usual pace, there would be a greatly exaggerated katabolic action and these children would handle their protein as do patients with Cushing's syndrome. We know they do not. I have shown recently that these hypopituitary dwarfs have a deficient production of hydrocortisone (Hubble 1957).

COMPETITION FOR PROTEIN IN PRIMARY HYPOPITUITARY DWARFISM

$G + T + I + A > H$: Normal adolescent growth.
$T + I \quad \equiv H$: Protein equilibrium in primary hypopituitary dwarfism.

Equally in cretins and in hypothyroid children, in whom we assume an associated inactivity of the growth hormone, we might also expect gluconeogenesis, were it not for the defective production of hydrocortisone which accompanies hypothyroidism. The formula allows me to make one forecast. The babies of diabetic mothers are both larger and longer than they should be. This represents a victory for the protein anabolisers and therefore it cannot be due to hyperadrenocorticism, as some have suggested. It could relate, however, to an excess of the protein anabolisers—to the growth hormone and to insulin.

In the cellular metabolism of protein a pattern, constant over years, can be discerned which is better described as an equilibrium—the resultant of hormonal influences—and not as homœostasis. If we knew enough of cellular chemistry, it might be possible to say that the constancy of the plasma-proteins made possible the growth of cells and provided for their changing metabolic needs, and if this is so, Claude Bernard would again have been justified of his wisdom.

Endocrine Homœostasis

So far, in regard to homœostasis in the endocrine system, I have mentioned only that the discharge of adrenaline into the blood-stream excites the further secretion of corticotrophin, and that the rate of insulin-secretion is adjusted by the level of the circulating blood-sugar. A more complicated and therefore more vulnerable method of reciprocal control of hormonal production is used in other parts of the endocrine system.

Corticotrophin and thyrotrophin, secreted by the anterior hypophysis, stimulate the formation of hydrocortisone and thyroxine, which in turn regulate the secretion of corticotrophin and thyrotrophin. This reciprocal balance is a neat and satisfactory mechanism in health. Increased utilisation of hydrocortisone and thyroxine—the target hormones—by the cells results in a lower concentration of these hormones in the plasma reaching the hypothalamus, and more corticotrophin or thyrotrophin is secreted, until the activity of the adrenal cortex or the thyroid matches the body's needs and the circulating hormones return to their original level.

This reciprocal control—this feedback mechanism—is affected by many extrinsic influences.

We can omit the nervous influences which may directly affect the target glands, and assume that the target gland alters its hormonal output only when it is affected by disease or by the stimulation of its appropriate trophic hormone. We cannot, however, disregard the physiological factors which affect the output of the trophic hormone. These may come from the periphery, as in hypoglycæmia (which, as we have seen, causes an outflow of adrenaline which stimulates corticotrophin), or as in the rabbit (which ovulates after genital stimulation), in the hen (whose egg-laying is enhanced by exposure to light, particularly when it is red), and in women and those animals in which suckling stimulates lactation. These physiological stimuli also, however, arise in the higher centres—as in the initiation of the sexual changes of puberty. The output of these trophic hormones is also affected by psychological states, as in the amenorrhœa which is common in girls placed in an unusual or difficult environment, and, as is accepted by most observers, in the emotional states which initiate the changes of thyrotoxicosis. Organic disease affects the hypophysis but rarely, and the hypothalamus less commonly still, but in those unfortunates in whom this central control fails, the target glands are left without any alternative stimulus for the production of their hormones.

Let us now examine a few of the consequences of disease upon endocrine homœostasis. When the pituitary fails from any cause, there is failure of trophic-hormone production in varying sequence. Sexual function fails

first, and it is usual for thyroid function to fail next. Occasionally, however, some degree of adrenocortical failure can be demonstrated when thyroid function appears normal by all available tests. A small degree of autonomic activity may persist in the thyroid and adrenal cortex for some time, despite pituitary failure, and the production of the electrolyte hormone (aldosterone) from the adrenal cortex is not under direct pituitary control. The chemical explanation for this sequence of failure is not yet known, but we may see a biological significance in it—the hormones of the adrenal cortex, which are most important for survival, are the most tenaciously preserved, while the hormones least important for survival, the sexual hormones, are the first to disappear. It will be agreed that a duplication of mechanisms—both reciprocity of control and local autonomy—would have given the body a better chance of emergence from disease.

Diseases in which there is an increased activity of the target gland show surprising derangements of homœostasis. It is assumed that sometimes these hyperplasias take origin from an excess of the trophic stimulus, which continues despite the excessive production of the target hormone. Examples of such diseases are Cushing's syndrome and thyrotoxicosis—and yet in both of them absence of the circulating trophic hormones from the plasma has been reported. This might be taken to mean that thyroxine and hydrocortisone, circulating in excess, have suppressed the formation of thyrotrophin and corticotrophin; but, if so, why does not the disease automatically abate—and, conversely, why is Cushing's syndrome sometimes relieved by irradiation of the pituitary? There are hypotheses formed to resolve these apparent dilemmas, but the conclusion for us is that the normal homœostatic control has been disrupted by disease.

When the target gland fails, as in myxœdema and Addison's disease, the homœostatic mechanism continues to operate and an increased quantity of corticotrophin and thyrotrophin are circulating. This continued prodding of a member of the band who is incapable of a full response is unworthy of the "leader of the endocrine orchestra," and it may be that this excessive stimulation by the trophic hormones contributes towards the eventual atrophy of the target gland. Who indeed "hath given understanding" to the hypophysis?

Principles of Homœostasis

The principles which have emerged from my superficial examination of these profound problems are:

(1) That homœostatic mechanisms were evolved as adaptive reactions to primitive environmental situations.

(2) That when the situation faced was both common and dangerous—as in hypoglycæmia—multiple mechanisms were evolved to deal with the hazard.

(3) That where the homœostatic responses are multiple, some are designed for the immediate reaction to an emergency, while others establish themselves as a long-acting mechanism.

(4) That plasma constancy is in contrast with changing cellular metabolism. The excess of protein anabolism over protein katabolism which permits the growth of the cell is governed by hormonal influences which ensure adequate protein for growth. This enduring pattern in the cellular metabolism of protein is better described as an equilibrium than as homœostasis.

(5) That when the pituitary trophic hormones fail, and for whatever reason, those hormones go first which have least influence on the capacity of the body to survive.

(6) That the pituitary-trophic/target-hormone method of control (the feedback mechanism) is easily deranged both by psychogenic and by pathological influences, and where the body wishes to maintain inviolate its most vital functions—for example, electrolyte control, growth and insulin production—other methods of control have been evolved.

Conclusions

One practical conclusion emerges from this discussion. It is that these homœostatic reactions will assist us in treatment only of those diseases which reproduce the primitive biological situation which these mechanisms were evolved to control—and of these the only example given here has been hypoglycæmia. More commonly these processes conflict with our therapeutic intentions. Sometimes they operate to worsen the condition of the patient. The surgeons and anæsthetists have, however, recently redressed this adverse balance by using the poikilothermic reaction in the treatment of disease.

There is, also, an inescapable physiological conclusion. It is this. That while the traditional expressions (homœostasis and fixity of the internal environment) have been rightly used to describe the ultimate objective of these myriad processes, the final impression is one of restless movement—movement from the carbohydrate stores and the tissue proteins to maintain the blood-sugar; movement of the amino-acids into cells insistent on the paramount needs of growth and reproduction; movement of hormones into the blood to maintain an equilibrium between the hypophysis and its subsidiary glands.

The ants on their hills, the stars in their courses, the dance of electrons, the play of children—these would be fitting similes to describe the unresting changes which ensure the body's internal constancy. Movement, not stasis, is both the condition and the sign of the free life.

REFERENCES

Ansell, B. M., Bywaters, E. G. L. (1956) *Ann. rheum. Dis.* **15**, 295.
Bearn, A. G., Billing, B. H., Sherlock, S. (1952) *Clin. Sci.* **11**, 151.
Bridge, E. M., Holt, L. E. jun. (1945) *J. Pediat.* **27**, 299.
Cannon, W. B. (1932) The Wisdom of the Body. London.
Gamble, J. L. (1954) Chemical Anatomy, Physiology and Pathology of Extracellular Fluid, Cambridge, Mass.
Hubble, D. (1956) *Brit. med. J.* i, 875.
— (1957) *Ibid*, i, 601.
— Illingworth, R. S. (1957) *Arch. Dis. Childh.* (in the press).
Long, C. N. H. (1952) *Lancet*, i, 325.
McCance, R. A., Young, W. F. (1941) *J. Physiol.* **99**, 265.
Smith, H. W. (1932) *Quart. Rev. Biol.* **7**, 49.
Talbot, N. B., Sobel, E. H., McArthur, J. W., Crawford, J. D., (1952) Functional Endocrinology. Cambridge, Mass.; p. 546.
van Creveld, S. (1952) *Arch. Dis. Childh.* **27**, 113.

CHEMOTHERAPY FOR STAPHYLOCOCCUS AUREUS

COMBINED USE OF NOVOBIOCIN AND ERYTHROMYCIN AND OTHER METHODS IN THE TREATMENT OF BURNS

E. J. L. LOWBURY
D.M. Oxfd

From the Medical Research Council Industrial Injuries and Burns Research Unit, Birmingham Accident Hospital

SHORTLY after chlortetracycline was introduced, it was found by controlled trials of systemic and local therapy to have some value in the treatment of staphylococcal infection of burns (Lowbury, Topley, and Hood 1952). A few weeks after the trial began, however, chlortetracycline-resistant staphylococci appeared, and they soon became predominant in the Burns Unit. Since then several new antibiotics active against *Staphylococcus aureus* have been introduced, but the organism has proved capable of producing variants resistant to all of those which can safely be administered by systemic routes.

In the treatment of certain infections, notably tuberculosis, the emergence of resistant variants can be delayed by the concurrent use of two or more unrelated agents (Medical Research Council 1953, Garrod 1953). The present paper describes an attempt to make use of this principle in the treatment of infected burns. The individual value of erythromycin and of novobiocin in the treatment of staphylococcal infection has been reported by many workers (see, for example, Herrell 1955, Martin et al. 1956, Nichols and Finland 1956, Rutenburg et al. 1956). Although resistance to each of these antibiotics is readily acquired by staphylococci, there is no relationship of cross-resistance between them (Garrod and Waterworth 1956, Wilkins et al. 1956). The paper also includes some data on the local use of chloramphenicol, and a note on the local pathogenicity of *Staph. aureus* in burns.

Emergence of Resistance to Novobiocin and Erythromycin in Vitro

Cultures of *Staph. aureus* sensitive to erythromycin and to novobiocin were isolated from the noses of 5 members of the staff. Single colonies were picked to nutrient broth, which was incubated at 37°C for eighteen hours. Single drops (0·02 ml.) of the undiluted broth culture were transferred to 1·0 ml. amounts of broth containing a range of doubling dilutions (0·1 to 100 μg. per ml.) of erythromycin ('Ilotycin') and of sodium novobiocin ('Albamycin'), each separately and the two in combination.

The three ranges of tubes were incubated at 37°C overnight, and the lowest concentration showing no turbidity (minimal inhibitory concentration, or M.I.C.) was noted. After this, daily subculture to a short range of two concentrations was made, the highest concentration which showed growth being subcultured to the same concentration and to double that concentration of the same antibiotic or mixture. Subculturing was continued for twenty days or until the M.I.C. was greater than 100 μg. per ml. At the end of this time each strain was tested by the tube dilution method (one drop of undiluted culture to each tube) for sensitivity to each of the antibiotics and to the mixture. The staphylococci were phage-typed by the method of Williams and Rippon (1952) at the beginning and again at the end of the series of subcultures. Sixteen serial transfers in broth of the staphylococci which had acquired resistance to the antibiotics were made in order to detect reversion to sensitivity.

RESULTS

The essentials are summarised in table I. "Day when resistance began to appear" is defined as the day on which the organism first grew in the original M.I.C. of antibiotic, provided further subcultures did not show reversion to a lower M.I.C.

Resistance appeared promptly (usually in one or two days) and mounted rapidly when the staphylococci were subcultured in the presence of either antibiotic alone. When subcultures were made in the presence of a mixture of the two antibiotics, there was a consistent delay in the first appearance of resistance until the sixth or seventh day, after which it mounted at approximately the same rate as in the presence of one antibiotic. The final M.I.C. after twenty subcultures in the mixture was consistently lower than it was after subculture in either antibiotic alone.

Strains subcultured in the presence of erythromycin and novobiocin alone acquired resistance only to the antibiotic with which they were cultured; those which were subcultured in the presence of both antibiotics always acquired resistance to both antibiotics, the final M.I.C. of erythromycin being consistently higher than that of novobiocin.

Phage-typing showed that each of the five strains of *Staph. aureus* had a different pattern of lysis (by undiluted phages 75/75B, 31A/75, 47A/53/75A/75B, 52A/80 and 80); all but one of these strains were untypable after twenty subcultures in the presence of novobiocin or erythromycin.

TABLE I—ACQUIRED RESISTANCE OF *Staph. aureus* ON DAILY SUBCULTURE WITH NOVOBIOCIN, ERYTHROMYCIN, AND BOTH ANTIBIOTICS TOGETHER IN THE MEDIUM

Strain	Initial M.I.C. (μg. per ml.)			Day when resistance began to appear			M.I.C. after 20 daily subcultures		
	Novobiocin	Erythromycin	Novobiocin and erythromycin	Novobiocin	Erythromycin	Novobiocin and erythromycin	Novobiocin	Erythromycin	Novobiocin and erythromycin
S 227	0·8	0·2	0·2	1	3	7	100	>100	12·5
S 160	0·4	0·2	0·2	1	1	6	>100	>100	50
S 230	0·4	0·2	0·2	1	2	6	>100	>100	50
S 210	0·8	0·2	0·2	1	2	6	>100	>100	25
S 202	0·8	0·2	0·2	4	2	6	>100	>100	100

Three of the five strains rendered resistant to erythromycin showed some reversion towards sensitivity on subculture in the absence of that antibiotic; all five of the novobiocin-resistant strains kept their full resistance after similar subcultures.

Therapeutic Trial of Novobiocin and Erythromycin

The purpose of this trial was: (*a*) to assess the therapeutic value of concurrent systemic administration of novobiocin and erythromycin in patients whose burns were colonised by *Staph. aureus* sensitive to these antibiotics, and (*b*) to test the effect of using this mixture of antibiotics on the incidence and emergence of staphylococci resistant to either or both of them. When the trial began no novobiocin-resistant staphylococci could be detected in the ward, but a proportion of the staphylococci (about 12%) were resistant to erythromycin.

Conduct of the Trial

On clinical grounds it was found impracticable to arrange a trial in which controls were selected on a random basis during the period of the trial. Oral novobiocin and erythromycin were therefore used concurrently instead of erythromycin alone (Lowbury and Cason 1954) for the routine chemotherapy of all infections with *Streptococcus pyogenes* during a period of three months; no patients were treated with either antibiotic alone. All patients whose burns showed the presence of *Strep. pyogenes* and also of *Staph. aureus* sensitive to novobiocin and erythromycin were admitted to the trial. The "controls" were patients treated in the same unit during the previous two years whose burns were colonised by *Strep. pyogenes* and a tetracycline-resistant *Staph. aureus*, and who received tetracycline therapy for the streptococcal infection. Their comparability with the novobiocin-erythromycin series was tested by reference to several criteria (odd and even hospital numbers, males and females, ages, estimated area of burns) in none of which was any significant difference between the two groups apparent.

In addition to this comparison of patients treated with novobiocin-erythromycin mixture and selected controls, we obtained some data for comparison from patients treated with erythromycin and with novobiocin alone.

The former were patients treated in the Burns Unit for streptococcal infection during the previous year, whose burns yielded erythromycin-sensitive *Staph. aureus* at the beginning of the course of erythromycin. The novobiocin-treated patients, who were selected after the trial of novobiocin and erythromycin was concluded, had novobiocin-sensitive staphylococci in their burns at the beginning of the course of therapy; their numbers are small, but it was thought unwise to extend the series in view of the increased resistance to novobiocin of many staphylococci isolated from patients in the ward.

Administration and Dosage of the Antibiotics

On the isolation from a burn of *Strep. pyogenes* (streptococcus classified as group A by Lancefield's method), a course of oral tetracycline, erythromycin, novobiocin, or novobiocin and erythromycin was started. The course continued for six days, and was occasionally extended.

Adult dosage of the antibiotics under investigation was: erythromycin (tablets) 300 mg. six-hourly; novobiocin (capsules) 500 mg. twelve-hourly. The same dosage of each antibiotic was used whether they were given singly or in combination. The antibiotics were given to children as flavoured suspensions at reduced dosage (a quarter of the adult dose between 1 and 3 years, half-dose between 3 and 5 years, and three-quarters between 5 and 10 years).

Local Treatment

The majority of the eligible patients were treated by the "closed" method. Penicillin cream, 1000 units per gramme, was applied on most burns at every change of dressings (about every fifth day, or more frequently if there was much exudate). This was generally continued until the time of skin-grafting or until the burn was healed. Tulle gras or polymyxin cream was applied on some burns instead of penicillin cream. The "exposure" method was used throughout on some of the burns, with repeated local insufflation of penicillin-lactose powder (10,000 units per g.); others were exposed shortly before healing, after they had been treated by the closed method.

Dressings were changed in an air-conditioned dressing-station, and the methods of Colebrook were followed with few modifications (Colebrook 1950).

Bacteriological Sampling and Control

Moist swabs were taken from burns at all changes of dressings and operations, or daily if the exposure method was used; they were inoculated on horse-blood-agar (with 4% New Zealand agar) and in Robertson's cooked meat broth.

The examination for bacteria was carried out as described previously (Lowbury et al. 1952). All gram-positive cocci were tested by a tube coagulase method: coagulase-positive strains were called *Staph. aureus* (or simply "staphylococci"). Nose and throat swabs, taken on admission and weekly from patients in the novobiocin-erythromycin trial, were also examined for *Staph. aureus*. All staphylococci isolated from patients during the trial were tested for sensitivity to several antibiotics, including novobiocin, erythromycin, and tetracycline, by a ditch-plate method with sensitive and resistant controls (see Topley, Lowbury, and Hurst 1951); we have, for convenience, tabulated as "sensitive" only those strains which showed a zone of inhibition approximately equal to that shown by the sensitive control. A number of strains were also tested by a tube dilution method (see above). The exudate from a number of burns was tested for the presence of each antibiotic by a disc method (Topley et al. 1951) on two strains of *Staph. aureus*, one rendered resistant to erythromycin, the other to novobiocin. The majority of the staphylococci were phage-typed.

Clinical Assessment

The results of skin-grafting in patients who were receiving or had received antibiotic therapy were obtained from the case-notes. A special watch was kept for rashes, nausea, vomiting, diarrhœa, abnormalities of the urine, and other signs of toxicity.

RESULTS

Table II shows the presence or absence of *Staph. aureus* in burns of patients treated by the closed method who were receiving or had just received a course of antibiotic therapy, together with results in the untreated controls. Swabs from all the burns included in the trial showed a moderate or heavy growth of *Staph. aureus* (on solid medium) at the beginning of the trial period; in the periods 1–7 days and 8–14 days, however, "*Staph. aureus* present" included also small numbers of staphylococci only detected on subculture from cooked meat broth.

Staph. aureus persisted in the burns during and after the period of treatment in a significantly smaller proportion of patients treated with the mixture of novobiocin and erythromycin than in the control patients. The differences were more striking even than these figures suggest, for a larger number of burns with persistent staphylococci in the treated than in the control series showed growth only on subculture from cooked meat broth. A minority of the persistent staphylococci in this series were sensitive to novobiocin and erythromycin, even in the earlier sampling period (days 1–7).

The slight but significant effect of erythromycin therapy on staphylococcal colonisation was consistently (and during days 1–7 significantly) smaller than that of the mixture; 26 out of 41 (63%) of the burns in the erythromycin series and 15 out of 49 (31%) of the burns in the novobiocin-erythromycin series retained their staphylococci during days 1–7 of therapy ($\chi^2 = 8{\cdot}35$, $P<0{\cdot}01$). Of the staphylococci which persisted under treatment, there was an appreciably greater proportion of sensitive strains in the erythromycin series than in the novobiocin-erythromycin series; this finding is consistent with the smaller therapeutic effect of erythromycin.

The number of patients treated with novobiocin alone was too small for significant comparisons with the control series, but the trend was unpromising. Out of 14 burns in this series, 11 (78%) retained *Staph. aureus* during days 1–7, and 10 of these were sensitive to novobiocin.

A small number of patients treated by the exposure method were given novobiocin and erythromycin for the

TABLE II—PERSISTENCE OF *Staph. aureus* DURING AND AFTER ANTIBIOTIC THERAPY FOR SENSITIVE STRAINS, IN BURNS TREATED BY THE CLOSED METHOD

Oral antibiotic therapy		*Staph. aureus* on: days 1 to 7				*Staph. aureus* on: days 8 to 14			
		Present	Absent	Significance of difference between treated patients and controls		Present	Absent	Significance of difference between treated patients and controls	
				χ^2	P			χ^2	P
Novobiocin and erythromycin	Patients	10 (5 sensitive)	18	10·2	< 0·001	9 (4 sensitive)	11	Too few	
	Burns	15 (5 sensitive)	34	24·7	< 0·001	10 (4 sensitive)	22	9·5	< 0·01
Erythromycin	Patients	17 (13 sensitive)	11	Not significant		13 (5 sensitive)	5	Not significant	
	Burns	26 (18 sensitive)	15	5·5	< 0·05	25 (8 sensitive)	7	Not significant	
Novobiocin	Patients	7 (6 sensitive)	3	Too few		3 (2 sensitive)	1	Too few	
	Burns	11 (10 sensitive)	3	Too few		4 (3 sensitive)	1	Too few	
Controls	Patients	18	3	..		14	3	..	
	Burns	28	3	..		19	6	..	

TABLE III—PERSISTENCE OF *Staph. aureus* DURING AND AFTER ANTIBIOTIC THERAPY IN BURNS TREATED BY THE EXPOSURE METHOD

Oral antibiotic therapy		*Staph. aureus* on :			
		days 1 to 7		days 8 to 14	
		Present	Absent	Present	Absent
Novobiocin and erythromycin	Patients	6 (4 sensitive)	3	3 (1 sensitive)	2
	Burns	8 (5 sensitive)	4	5 (1 sensitive)	2
Controls	Patients	12	1	11	0
	Burns	13	1	13	0

treatment of streptococcal infections. The persistence of *Staph. aureus* in this series is shown beside that of a series of controls in table III. Of 12 exposed burns treated with novobiocin and erythromycin, 8 failed to lose *Staph. aureus*, and 5 of these yielded staphylococci sensitive to both antibiotics. In view of these unpromising results and of the fact that novobiocin-resistant staphylococci appeared first in exposed burns, the trial on patients treated by the exposure method was discontinued.

Emergence of Resistant Staphylococci

The sensitivity to novobiocin and to erythromycin of all staphylococci isolated from patients in the burns wards week by week during the trial and for two weeks before it started are shown in table IV. During the first four weeks of the trial there was a progressive fall in the proportion of erythromycin-resistant staphylococci, though more erythromycin was being used then (on 7 cases, in combination with novobiocin) than had been used alone in the previous four weeks (3 cases treated). In the second week of the trial, novobiocin-resistant staphylococci appeared in a patient treated by the exposure method, and were isolated on repeated swabbings from the same patient. In the fifth week staphylococci resistant to both antibiotics began to appear and then increased in frequency from week to week. Strains resistant to novobiocin alone appeared rarely, and there was no consistent increase in the proportion of strains resistant to erythromycin alone. A few patients who were not receiving erythromycin and novobiocin were found to have organisms resistant to both antibiotics in their burns during the later part of the trial. This showed that cross-infection with resistant organisms was occurring, and cross-infection probably accounted for the appearance of resistant staphylococci in some of the patients receiving chemotherapy.

TABLE IV—NOVOBIOCIN AND ERYTHROMYCIN SENSITIVITY OF *Staph. aureus* IN BURNS BEFORE AND DURING TRIAL OF CONCURRENT THERAPY WITH THESE ANTIBIOTICS (STARTED SEPT. 18, 1956)

Weeks during 1956	Percentage staphylococci from burn swabs				Total no of staph.
	Sensitive to novobiocin and erythromycin	Sensitive to novobiocin : resistant to erythromycin	Resistant to novobiocin : sensitive to erythromycin	Resistant to novobiocin and erythromycin	
Sept. 1–7 ..	79·5	20·5	0	0	98
„ 8–14 ..	82	18	0	0	89
„ 15–21 ..	87·5	12·5	0	0	137
„ 22–28 ..	86·6	8·9	4·5	0	90
Sept. 29–Oct. 5	93·9	4·1	2	0	98
Oct. 6–12 ..	92·1	7·9	0	0	140
„ 13–19 ..	85·8	11·1	0	3·1	162
„ 20–26 ..	77·7	13·2	0	9·1	121
Oct. 27–Nov. 2	69·8	13·4	0	16·8	149
Nov. 3–9 ..	78·7	3·5	0	17·8	113
„ 10–16 ..	67·4	11·9	1·1	19·6	92
„ 17–23 ..	73·3	6·2	0	20·5	161
„ 24–30 ..	75	9·2	1·3	14·5	152
Dec. 1–7 ..	65·6	10·2	0·8	23·4	128

Tube dilution tests showed that the minimal inhibitory concentration of erythromycin for resistant strains was usually more than 100 μg. per ml. The novobiocin-resistant strains were always much more sensitive than this, being inhibited by 10 μg. and sometimes by 5 μg. novobiocin per ml.

Sensitivity of Staphylococci Carried by Staff

On three occasions during and shortly after the trial of novobiocin and erythromycin, nose and throat swabs were taken from all members of the staff, including nurses and doctors. 30 swabs yielded *Staph. aureus*; 3 of these were resistant to erythromycin, 6 to tetracycline, and 6 to penicillin; all were sensitive to novobiocin.

Phage-types of the Staphylococci

All the novobiocin-resistant and erythromycin-resistant staphylococci that appeared in the burns were of phage-group III, many showing a pattern of lysis by numerous phages. In all but 2 of the patients such strains appeared in the place of novobiocin- and erythromycin-sensitive staphylococci of the same phage group, and their presence might have been due either to cross-infection or to the emergence of resistance under treatment.

Detection of Antibiotics in the Burn Exudate

In most of the burns tested it was possible to detect novobiocin, the zone of inhibition corresponding to that produced by a concentration of 1–5 μg. per ml. in the control disc. Erythromycin was more often not detected, or detectable only as a trace, though concentrations of approximately 1 μg. per ml. were detected in some burns.

Persistence of Staphylococci in the Nose

4 patients from whose nares *Staph. aureus* sensitive to novobiocin and erythromycin was isolated at the beginning of treatment with these antibiotics failed to lose them during the course of treatment. In 6 patients sensitive staphylococci were replaced by strains resistant to one or both antibiotics. No patients were cleared of nasal staphylococci during treatment.

Toxic Effects

2 patients receiving novobiocin vomited while under treatment. No other side-effects were observed in any patient.

TEST FOR SYNERGIC ACTION OF NOVOBIOCIN AND ERYTHROMYCIN

In the light of studies by Jawetz and others (see Jawetz 1952), it seemed unlikely that novobiocin and erythromycin would act synergically on sensitive bacteria, since both antibiotics are predominantly bacteriostatic in their mode of action. There was no suggestion from the tests reported above that the bacteriostatic action of these antibiotics was either potentiated or inhibited by use in combination. Two strains of *Staph. aureus* sensitive to both antibiotics (the Oxford strain and one isolated from a burn) were tested for bactericidal synergism as follows :

Both strains were first tested for sensitivity to novobiocin and to erythromycin by the tube dilution test described above. Tubes containing the minimal inhibitory and higher concentrations were subcultured to blood-agar after eighteen hours at 37°C; the dilutions from which no growth was obtained were considered to show bactericidal action, and the following tests were made with broth containing the smallest bactericidal concentrations of the antibiotics (25 μg. erythromycin per ml. and 12·5 μg. novobiocin). Tubes of broth containing these concentrations of the antibiotic alone and in combination were inoculated with 0·02 ml. of eighteen-hour broth cultures of each of the two staphylococci. Immediately after addition of the bacteria, and again after three hours, six hours, and twenty-four hours at 37°C, viable counts of staphylococci in the antibiotic broth were made by the method of Miles et al. (1938). Tests were also made

with a mixture containing erythromycin and novobiocin, each at half its minimal bactericidal concentration.

There was no evidence that either staphylococcus was killed more rapidly by the mixture of antibiotics than by each of the antibiotics used alone. One strain (the Oxford staphylococcus) showed a higher count after six hours and twenty-four hours in the mixtures than with either antibiotic by itself. Synergic action was, therefore, unsupported by in-vitro observation.

Alternative Methods for Removal of Staphylococci from Burns

Because of the risks of selecting staphylococci resistant to erythromycin and novobiocin, it is important that this form of treatment should be used only when there is an important clinical indication for it, and that alternative methods should be available. Flint et al. (1952) reported successful treatment of infected wounds with local applications of chloramphenicol, and Liedberg, Reiss, Kuhn, et al. (1955) found that local chloramphenicol had prophylactic and therapeutic effects against *Strep. pyogenes*. We have made two small controlled trials of the use of chloramphenicol cream in the treatment of staphylococcal infection of burns. Such a study seemed feasible because chloramphenicol is seldom used in this unit for systemic therapy, and the large majority of staphylococci isolated here have been sensitive to the antibiotic.

The first trial was a pilot study on 17 inpatients.

Burns colonised by *Staph. aureus* sensitive to chloramphenicol and resistant to penicillin were, when possible, allocated alternately to penicillin and to chloramphenicol treatment groups. In the former group (controls), the burns were dressed with penicillin cream, 1000 units per g. in a 'Lanette' wax base with glycerol (Clark et al. 1943); in the latter group they were dressed with a cream containing chloramphenicol (10 mg. per g.), the antibiotic being dissolved in propylene glycol before it was mixed with the cream from which glycerol was omitted. Three applications were made on alternate days.

Swabs taken at the time of dressing showed that 8 out of 9 patients treated with chloramphenicol lost their staphylococci under treatment, as compared with 1 out of 8 controls treated with penicillin cream.

The second trial was prompted by this promising result and by the observations of Dr. A. Moselhi in a clinical comparison on outpatients. During a period of six months 121 outpatients were allocated to two treatment groups by hospital number, the odd-numbered receiving penicillin cream and the even-numbered receiving chloramphenicol cream at every dressing. Although an appreciable proportion of staphylococci isolated from outpatient burns were sensitive to penicillin, a previous trial (Jackson, Lowbury, and Topley 1951a) had shown that the application of a cream containing 1000 units penicillin per gramme is likely to have little value in the treatment of burn infections with sensitive staphylococci. The penicillin-treated patients were therefore regarded as "controls."

Burns were swabbed at change of dressings (usually once a week) and examined by the methods described above. *Staph. aureus* appeared in 55 patients—less often and also less continuously than it is found in the burns of inpatients. To compare the effectiveness of the two creams in removing *Staph. aureus* from the burns, the number of occasions on which a positive swab result was followed by another positive or by a negative result were compared in the two groups. Out of 29 samplings in patients treated with chloramphenicol cream, 17 showed successful clearance of *Staph. aureus*, as compared with 6 out of 22 staphylococcal infections cleared after application of penicillin cream. This difference was just below the level of statistical significance ($\chi^2 = 3{\cdot}73$, $P > 0{\cdot}05$), but taken together with the findings in the pilot study it suggested that chloramphenicol cream was having some therapeutic effect against *Staph. aureus*. The effect was undoubtedly smaller in outpatients than it would have been in a similar number of inpatients, because of longer intervals between dressings, less perfect cover, and less frequent colonisation of burns with *Staph. aureus*.

Resistant staphylococci appeared on the burns of 3 outpatients and 1 inpatient treated with chloramphenicol cream.

TABLE V—RESULTS OF SKIN-GRAFTING AND THE CONTROL OF *Staph. aureus* IN BURNS

Controlled trial	Group	Split-skin graft "take"			
		80–100%	<80%	χ^2	P
Oral chlortetracycline (for primary excision and grafting) 1950	Treated	16	2	4·72	<0·05
	Controls	9	9		
Oral chlortetracycline (for delayed grafting) 1950	Treated	16	5	Not significant	
	Controls	24	14		
Local chlortetracycline 1951	Treated	65	14	4·75	<0·05
	Controls	43	23		
Local chlorhexidine ('Hibitane') 1955	Treated	27	9	6·82	<0·01
	Controls	12	18		
Novobiocin and erythromycin 1956	Treated	19	8	Not significant	
	Controls (tetracycline)	6	7		

A Note on the Pathogenicity of Staphylococci in Burns

When *Strep. pyogenes* appears on a burn there is an urgent indication for chemotherapy, especially if the area is to receive skin-grafts. *Staph. aureus*, by contrast with the streptococcus, is found in the great majority of burns treated in hospital, and it usually has no obvious pathological effects. Liedberg, Reiss, and Artz (1955) have shown on the rabbit that *Staph. aureus* may interfere with the take of skin-grafts, but the effect of the staphylococcus in their experiments was smaller than that of *Pseudomonas pyocyanea* and still smaller than that of *Strep. pyogenes*. Jackson et al. (1951b) found that the results of skin-grafting and the healing time were significantly better in burns treated with polymyxin cream than in untreated controls during a prophylactic trial of the antibiotic. They argued from this that *Ps. pyocyanea* and some other polymyxin sensitive coliforms, which are often dismissed as saprophytes, may nevertheless interfere with the take of skin-grafts.

Table v shows the results of split skin-grafts in burns during trials of various forms of chemotherapy or prophylaxis for *Staph. aureus*. In each trial the skin-graft results were better in the patients who had received chemotherapy or prophylaxis than in the controls; each agent—oral and local chlortetracycline (Lowbury et al. 1952), local chlorhexidine (Lowbury 1955), and novobiocin and erythromycin—was also found to have some therapeutic or prophylactic action against *Staph. aureus* in the burns and little or none against the gram-negative bacilli. In each of the trials both treatment and control groups were receiving comparable treatment for *Strep. pyogenes*. The findings resemble those previously recorded in the prophylactic trial of polymyxin, and suggest that control of *Staph. aureus* may have a beneficial effect on the healing of burns. The local pathogenicity of the staphylococcus is small compared with that of *Strep. pyogenes*, and chemotherapy (e.g., with novobiocin and erythromycin) is indicated only in selected cases. There is, however, a stronger case for prophylaxis by local application of certain chemotherapeutic agents (e.g., neomycin, bacitracin, chlorhexidine) and by the maintenance of a high standard of aspectic discipline.

Discussion

Staphylococci resistant to novobiocin or to erythromycin emerged more slowly when a sensitive strain was grown in the presence of a mixture of these antibiotics than when it was grown in the presence of either alone. If advantage is to be taken of this principle, it is important that mutants resistant to one antibiotic only should be destroyed or inhibited by the other agent in the therapeutic mixture; in other words, chemotherapy must be able to eliminate a sensitive strain of the organism in question. In our previous experience, *Strep. pyogenes* had been the only organism which systemic chemotherapy (with oral tetracyclines or erythromycin) would regularly eliminate from burns, and we therefore did not expect that the emergence of staphylococci resistant to erythromycin and novobiocin would be appreciably delayed by combined chemotherapy with these agents. Hence the fall in the incidence of erythromycin-resistant strains during the first weeks of the trial was gratifying. Nevertheless, slight or moderate resistance to novobiocin, at first alone but later almost always associated with erythromycin resistance, appeared at an earlier stage of the trial than erythromycin resistance had appeared in earlier trials of that antibiotic.

In the earlier patients of the trial, who were also treated by the closed method, initial success in keeping down the incidence of resistant strains was undoubtedly due to the prompt elimination of *Staph. aureus* during combined chemotherapy with novobiocin and erythromycin. The effectiveness of the combination seemed to be greater than that of either antibiotic by itself, and approached that of erythromycin and of the tetracyclines against *Strep. pyogenes*. Unlike *Strep. pyogenes*, however, *Staph. aureus* usually failed to respond to chemotherapy when burns were treated by the exposure method, and resistant strains emerged in these patients and soon spread to others, including some who had not received the antibiotics.

In spite of its potential value in the treatment of staphylococcal infection, the use of novobiocin and erythromycin is clearly undesirable in the treatment of burns unless there is an important clinical indication for it. Staphylococci appear to have some local pathogenic action in burns; our studies suggest that they sometimes interfere with the take of split-skin grafts, and the α toxin is shown to be damaging to skin cells in vitro (J. C. Lawrence, personal communication). Excellent results are, nevertheless, commonly obtained when *Staph. aureus* is present in burns. When it seems necessary to remove staphylococci it might be considered preferable first to try chloramphenicol cream (1%) under dressings. A limited experience suggests that neomycin, bacitracin, and chlorhexidine, which can be applied locally, are probably less effective than chloramphenicol in removing staphylococci from the burned surface; two of these agents (neomycin and chlorhexidine), however, were tested and found to have some prophylactic value, and even when they were used for long periods, in routine applications, no resistant staphylococci emerged.

The principal use of erythromycin in this unit has been for the elimination of *Strep. pyogenes* (especially tetracycline-resistant strains) from burns, and during this treatment erythromycin-resistant staphylococci are liable to appear. In these circumstances novobiocin is reserved as the agent of choice for the treatment of staphylococcal sepsis, preferably in combination with erythromycin if the staphylococcus is sensitive to both agents. In other fields, where erythromycin is used primarily as an agent for the treatment of staphylococcal infection and where cross-infection is less liable to occur than it is in a burns unit, the combination of novobiocin and erythromycin may prove of outstanding value both for its therapeutic powers and for its tendency to delay the emergence of resistant mutants.

Summary

(1) Five strains of *Staph. aureus* sensitive to novobiocin and erythromycin acquired resistance more rapidly when grown in a medium containing either antibiotic alone than they did in the presence of a mixture of the two.

(2) In a trial of combined therapy with novobiocin and erythromycin, *Staph. aureus* was cleared from a higher proportion of covered burns treated with these antibiotics (34 out of 49, 68%) than from comparable burns receiving no chemotherapy (3 out of 31, 10%). The therapeutic effect of the mixture was significantly greater than that of erythromycin used alone, and also greater than that of novobiocin used alone in a small series of burns. Patients treated by the exposure method did not usually lose their staphylococci when receiving novobiocin and erythromycin. There was no evidence of synergic action of novobiocin and erythromycin against staphylococci in vitro.

(3) The incidence of erythromycin-resistant staphylococci fell during the first four weeks of a period when erythromycin and novobiocin were being used only in combination. Minor degrees of resistance to novobiocin began to appear in the second week of this trial, and there was a gradual increase in the numbers of staphylococci resistant to erythromycin and slightly resistant to novobiocin from the fifth week onwards. Resistance to novobiocin first appeared in a patient treated by the exposure method.

(4) Local application of chloramphenicol cream (1%) in a base containing propylene glycol appeared to have some therapeutic value against *Staph. aureus* in the burns of outpatients.

(5) In several trials which showed a selective prophylactic or therapeutic action against *Staph. aureus*, the results of skin-grafting were better in treated patients than in the controls. The local pathogenicity of *Staph. aureus*, however, is insufficient to warrant routine chemotherapy against the organism in burns.

I wish to thank Dr. A. Moselhi for suggestions on the local use of chloramphenicol; Mr. L. Hurst, F.I.M.L.T., Mr. H. A. Lilly, A.I.M.L.T., and Miss G. Hogg for laboratory work; Dr. J. Dugger and Upjohn of England Ltd., for supplies of novobiocin; Mrs. M. Kilner for secretarial assistance; and my colleagues and the nursing staff of the Burns Unit for their coöperation.

REFERENCES

Clark, A. M., Colebrook L., Gibson, T., Thomson, M. L., Foster, A. (1943) *Lancet*, i, 605.
Colebrook, L. (1950) A New Approach to the Treatment of Burns and Scalds. London.
Flint, M. H., Gillies, H., Reid, D. A. C. (1952) *Lancet*, i, 541.
Garrod, L. P. (1953) *Brit. med. J.* i, 953.
— Waterworth, P. M. (1956) *Ibid*, ii, 61.
Herrell, W. E. (1955) Erythromycin. Antibiotics Monographs no. 1. New York.
Jackson, D. M., Lowbury, E. J. L., Topley, E. (1951a) *Lancet*, ii, 705.
— — — (1951b) *Ibid*, p. 137.
Jawetz, E. (1952) *Arch. intern. Med.* **90**, 301.
Liedberg, N. C. F., Reiss, E., Artz, C. P. (1955) *Ann. Surg.* **142**, 92.
— — Kuhn, L. R., Amspacher, W. H., Artz, C. P. (1955) *Surg. Gynec. Obstet.* **100**, 219.
Lowbury, E. J. L. (1955) *Brit. med. J.* i, 985.
— Cason, J. S. (1954) *Ibid*, ii, 914.
— Topley, E., Hood, A. M. (1952) *Lancet*, i, 1036.
Martin, W. J., Heilman, F. R., Nichols, D. R., Wellman, W. E., Geraci, J. E. (1956) *Antibiot. Med.* **2**, 258.
Medical Research Council (1953) Tuberculosis Chemotherapy Trials Committee. *Brit. med. J.* i, 521.
Miles, A. A., Misra, S. S., Irwin, J. O. (1938) *J. Hyg., Camb.* **38**, 732.
Nichols, R. L., Finland, M. (1956) *Antibiot. Med.* **2**, 241.
Rutenburg, A. M., Shapiro, P., Schweinburg, F. (1956) *New Engl. J. Med.* **255**, 325.
Topley, E., Lowbury, E. J. L., Hurst, L. (1951) *Lancet*, i, 87.
Wilkins, J. R., Lewis, C. Barbiers, A. R. (1956) *Antibiot. & Chemother.* **6**, 149
Williams, R. E. O., Rippon, J. E. (1952) *J. Hyg., Camb.* **50**, 320.

ASSAY OF ANTIHÆMOPHILIC GLOBULIN IN TREATMENT OF HÆMOPHILIC PATIENTS

ROSEMARY BIGGS
M.D., B.Sc., Ph.D. Lond.
ASSISTANT PATHOLOGIST, RADCLIFFE INFIRMARY, OXFORD

THE success or failure of surgical treatment in hæmophilic patients depends on the level of antihæmophilic globulin (A.H.G.) in their blood achieved by transfusing plasma or concentrated A.H.G. Hæmophilic patients vary in the initial level and in the ease with which it can be raised. In general, it is our experience that if the A.H.G. level can be raised to more than 30% of normal, bleeding for 24–48 hours after operation is not excessive. In judging the dose of A.H.G. it is clearly important to have some reasonably reliable method for its measurement.

Most of the methods that have been used depend on assessing the ability of a sample to correct the abnormality of hæmophilic blood. Langdell, Graham, and Brinkhous (1950), and Langdell, Wagner, and Brinkhous (1953) have used the prothrombin consumption test or the partial thromboplastin time to assess the degree of correction. Pitney (1956) used the thromboplastin generation test. Wolf (1956) used a modified prothrombin consumption test. Biggs, Eveling, and Richards (1955), and Biggs and Macfarlane (1957a) used a direct assay of antihæmophilic globulin. The prothrombin consumption method of Langdell, Graham, and Brinkhous (1950) requires fresh hæmophilic blood in relatively large amounts and is therefore not practicable. The partial thromboplastin time is only very roughly quantitative and probably is not precise enough for the control of therapy. The direct assay described by Biggs and Macfarlane (1957a) is sufficiently reliable but may be difficult to standardise and interpret. The method now described is similar to that of Pitney (1956).

Technique

Reagents

$CaCl_2$.—M/20 and M/40 solutions are made up as described by Biggs and Macfarlane (1957a).

Dried serum is made and dissolved in glyoxaline buffer for use as described by Biggs, Eveling, and Richards (1955). The solution must stand for at least four hours before use and may be left at 4°C overnight.

Phospholipid is made as described by Biggs, Eveling, and Richards (1955). It is made up at a concentration of 25 mg. per ml. and diluted to give optimum results. The concentration required is greater than that used in the assay method of Biggs, Eveling, and Richards (1955). Usually a 1/50 dilution containing 0·5 mg. per ml. is satisfactory. The solution may be stored frozen at –20°C.

$Al(OH)_3$ is obtained as a moist gel from British Drug Houses and made up for use by suspending 1 g. in 4 ml. of distilled water.

Collection of Blood

All samples are collected by mixing 9 parts of blood with one part of 3·8% trisodium citrate and plasma obtained by centrifuging. If it is more convenient, plasma used as substrate may be collected in bulk and stored frozen solid at –20°C and used over a period of 2–3 weeks.

For the assay the samples are adsorbed with $Al(OH)_3$ by adding 0·1 ml. of the diluted gel to 0·9 ml. of plasma. The mixture is left at 37°C for 2 minutes; the $Al(OH)_3$ is then sedimented by centrifuging at 2000 r.p.m. for 10 minutes; and the clear supernatant plasma is decanted.

Standard Normal Plasma

Equal amounts (about 2·2 ml.) of blood from 4 normal subjects are collected into one 10 ml. centrifuge tube containing 1 ml. of 3·8% trisodium citrate. The total volume must be 10 ml. (9 ml. of blood and 1 ml. 3·8% citrate). The contents of the tube are mixed after each addition. The normal subjects may be patients from whom routine hæmatological samples are collected for other purposes, provided that the patients have no coagulation defect or thrombosing tendency. The plasma must be used on the day of collection.

Standard Hæmophilic Plasma

Citrated blood is collected from severely affected hæmophilic patients as these are encountered and the plasma is stored frozen solid at –20°C in 2 ml. amounts until required.

Technique

The method consists in carrying out the thromboplastin generation test on normal and hæmophilic $Al(OH)_3$-treated plasma and on mixtures of the two in known proportions. The samples are mixed and tested undiluted and thus no provision of factor V is required because this is present in both whole-plasma samples. The mixtures tested are:

Normal plasma	1	1	1	1	1
Hæmophilic plasma	3	7	15	31	63
Treated hæmophilic	1	1	1		
Untreated hæmophilic	0	1	3		

The 1-in-4 dilution is made by mixing 0·1 ml. of normal $Al(OH)_3$-treated plasma with 0·3 ml. of hæmophilic $Al(OH)_3$-treated plasma. The 1-in-8 dilution is made by taking 0·2 ml. of the 1-in-4 dilution and adding 0·2 of the hæmophilic sample. Other dilutions are made similarly by the doubling dilution method to economise in the use of hæmophilic plasma.

The test is then carried out as follows:

0·1 ml. of the $Al(OH)_3$-treated plasma is mixed with 0·1 ml. of phospholipid, 0·1 ml. of serum and 0·1 ml. of M/20 $CaCl_2$. A stopwatch is started on the addition of the $CaCl_2$. At 10, 15, 20, and 25 minutes, 0·1 ml. samples are tested as in the thromboplastin generation test by adding together with 0·1 ml. of M/40 $CaCl_2$ to 0·1 ml. of normal substrate plasma, the clotting-time of which is recorded. (Note the use of two concentrations of $CaCl_2$.) From this test two incubation times at which a minimum clotting is obtained are selected (e.g., either 15 and 20 minutes or 20 and 25 minutes). The other samples are similarly tested. It will be observed that 10 or 15 minutes elapses before any tests are taken and a gap of 5 minutes separates each clotting test. Thus it is possible to test 8–10 samples in two batches of tests to be completed in 35–40 minutes. The organisation required when minimum clotting-times occur at 20 and 25 minutes is outlined below.

The first mixture is completed by the addition of $CaCl_2$ as the stopwatch (called the incubation stopwatch) is started; its incubation therefore starts at time 0. The second mixture is made and the $CaCl_2$ added as the incubation stopwatch records 1 minute. Subsequent samples can be started to incubate at 2, 3, and 4 minutes as recorded by the incubation stopwatch. The incubation of five further samples can be started at 10, 11, 12, 13, and 14 minutes. To test each sample at 20 minutes samples are removed in series from the first batch of tubes at 20, 21, 22, 23, and 24 minutes: the 25-minute samples are removed at 25, 26, 27, 28, and 29 minutes. The second-batch samples are similarly taken at 30–39 minutes. The system is shown diagrammatically in table I.

TABLE I—OUTLINE OF THE ORGANISATION REQUIRED TO TEST 10 SAMPLES SIMULTANEOUSLY BY THE A.H.G. ASSAY METHOD (SEE TEXT)

Batches of samples	Times of starting incubation (min.)	Times of testing mixtures (min.)	Times after starting at which test is made (min.)
1	0, 1, 2, 3, 4	20, 21, 22, 23, 24 25, 26, 27, 28, 29	20, 25
2	10, 11, 12, 13, 14	30, 31, 32, 33, 34 35, 36, 37, 38, 39	20, 25

Following this system the dilution curve can be constructed and two hæmophilic samples can be tested in less than an hour.

TABLE II—RESULTS OF THE A.H.G. ASSAY METHOD CARRIED OUT ON A NORMAL SAMPLE AND ON SPECIMENS FROM TWO TREATED HÆMOPHILIC PATIENTS

Source of A.H.G.	Constitution of sample tested		Incubation time (min.)		Average result (sec.)	Result
	Proportion of hæmophilic plasma*	Proportion of A.H.G. containing plasma	20	25		
Normal	1	1	11·8	12·3	12·1	
	3	1	13·0	15·8	14·4	
	7	1	18·2	18·2	18·2	Normal dilution curve
Plasma	15	1	24·8	25·5	25·1	
	31	1	29·5	34·2	31·7	
	1	0	70·1	55·7	62·9	
Treated hæmophilic plasma (1)	0	1	13·4	15·0	14·2	
	1	1	15·6	19·4	17·5	28%
	3	1	18·4	21·2	19·8	
Treated hæmophilic plasma (2)	0	1	20·0	23·8	21·9	
	1	1	25·8	26·6	26·4	9%
	3	1	30·8	31·4	31·1	

* Plasma from a patient with no antihæmophilic globulin.

ASSESSMENT OF THE RESULTS

An example of the use of the test is shown in table II. The figures for the normal dilution curve may be plotted on double logarithmic paper when an approximately straight-line graph is obtained. The figures from the treated sample and the two dilutions in hæmophilic plasma are read from the graph and the results are averaged.

EXPERIENCE OF THE METHOD

Choice of Phospholipid

The phospholipid recommended is not quite so simple to prepare as the chloroform extract of brain described by Bell and Alton (1955). Using the chloroform-extracted brain, the thromboplastin-forming reaction proceeds very rapidly, and the minimum clotting-times are not sufficiently lengthened by dilution of normal with hæmophilic plasma. Thus the undiluted normal plasma may give results at 8–9 seconds and the 1-in-16 dilution 13–14 seconds, whereas using the more slowly acting phospholipid the corresponding difference might be 12–13 seconds for the undiluted normal plasma and 25–30 seconds for the 1-in-16 dilution.

Source of Serum

Freeze-dried serum is a very stable and active reagent. If the serum is collected from 500 ml. of whole blood, the same serum may be used for many months. It is probable that freshly collected serum can be used provided that the whole blood is incubated at 37°C over night before the serum is separated. Such sera can be stored at –20°C.

Standard Normal Plasma

One of the main difficulties in assaying antihæmophilic globulin is the selection of a standard for comparison

Biggs, Eveling, and Richards (1955) used a dried animal antihæmophilic globulin, but the method was used mainly for the comparison between different dried preparations and for clinical studies a direct comparison with normal plasma is necessary. Random selection of a normal sample must necessarily give very unreliable results because of the very wide range of variation between normal samples. Studying 58 samples we have confirmed the observations of Brinkhous et al. (1954) and Pitney (1956). Our results are given in fig. 1.

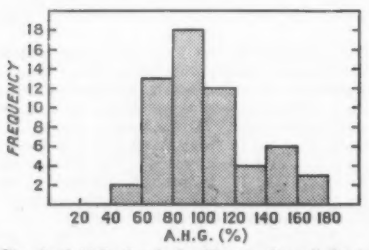


Fig. 1—A.H.G. levels in 58 samples of fresh normal human plasma expressed as percentage of average normal.

Brinkhous et al. (1954) and Pitney (1956) used one selected normal donor. This method is better than a random selection of the normal but has obvious disadvantages in routine work.

We have experimented with freeze-dried normal plasma and with wet samples frozen at –20°C. The freeze-dried specimens seem to deteriorate rapidly; the frozen samples sometimes maintain activity well for months but individual samples behave very variably. Neither of these procedures is sufficiently reliable. Preliminary observations seem to suggest that freezing at –30°C might give better results but few laboratories have apparatus designed to maintain this temperature.

From fig. 1 it will be seen that 80% of the observations on normal plasma fall in the range 60–140%. Very few are under 60% and rather more are over 140%. Random selection of normals from this range is bound to give extremely variable results; but, if the average of four normals were taken 80% of the means should fall within the range 80–120%. The average results for four normal subjects can be obtained quite easily by pooling equal volumes of blood from four patients attending the clinical laboratory for other tests. The likely range of error due to the random selection of normal samples is shown in table III. The method is not very precise and when a reliable method for storing a single normal sample is available this will be used in preference.

Use of Undiluted Plasma

Undiluted plasma does not behave in the thromboplastin generation test in exactly the same manner as diluted plasma. The undiluted plasma has an inhibitory effect giving longer clotting-times than diluted plasma for a given A.H.G. level. Thus the dilution curve of normal plasma in hæmophilic plasma gives a reasonable range of clotting-times between 1 in 4 and 1 in 64 dilutions. Results using undiluted plasma for treated hæmophilic patients tend to be lower than those of methods in which saline plasma dilutions are compared. Since the patients have undiluted plasma circulating, it is reasonable to suppose that results derived from whole plasma will be the most reliable.

TABLE III—EXPECTED RANGE OF VARIATION INTRODUCED INTO THE A.H.G. ASSAY METHOD BY USING A POOL OF 4 NORMAL SAMPLES AS THE CONTROL

(Column 1 shows hypothetical true values. Column 2 shows the effect of selecting a mixture of 4 normal subjects with an average value of 120%. Column 3 shows the results if the selected normal has a value of 80%)

True value	Minimum	Maximum	True value	Minimum	Maximum
5	4·1	6·5	30	25	37
10	8·3	12·5	35	29	43
15	12·4	18·6	40	33	50
20	16·6	25	45	37	56
25	20	31	50	41	65

Laboratory Control of Therapy with A.H.G. Preparations

The aim in treatment of hæmophilic patients is to raise the blood-A.H.G. to levels at which clotting may occur normally in surgically severed vessels: the lumen may then be occluded by clot at the time of suture. The opinion that A.H.G. levels above 30% of normal are necessary is based on the study of A.H.G. levels in mildly affected patients (Biggs and Macfarlane 1957b) and on the response of severely affected patients to treatment (Fraenkel and Honey 1955, Macfarlane et al. 1957, Wishart et al. 1957).

If a supposed hæmophilic patient requires surgery, the first step is to establish the diagnosis of hæmophilia

using the thromboplastin generation test (Biggs and Douglas 1953) and to determine the A.H.G. level in his blood before treatment starts. If he is severely affected then the level will be found to be less than 1%. If he is mildly affected levels up to 30% may be recorded. Appropriate treatment depends to some extent on the results of this initial test.

Experience with the use of plasma transfusion has shown that 1000 ml. of fresh plasma given intravenously in 45 minutes usually raises the A.H.G. level of a severely affected patient to between 18 and 30% of normal. At these levels the bleeding from minor surgery, such as dental extraction and the removal of nasal polypi, can be carried out with much less bleeding than in the untreated patient (Macfarlane et al. 1957, Wishart et al. 1957). For such procedures it should not generally be necessary to use animal A.H.G. When such an operation is contemplated it is wise to give 1000 ml. of plasma on the day before operation and to test the blood-level of A.H.G. 15 minutes after the transfusion is complete. If a circulating anticoagulant is present or if the patient is refractory to plasma transfusion this will be disclosed by the failure to obtain a satisfactory rise of A.H.G. level. The preliminary test transfusion should not be done several days prior to the surgical treatment because some resistance to transfusion may develop.

If the patient is mildly affected and the initial level of A.H.G. is more than 10%, then generally the administration of 1000 ml. of fresh plasma will raise the A.H.G. level to more than 30% and more serious surgery may be undertaken (see case 17 of Macfarlane et al. 1957). In these cases also it is wise to make a preliminary test of the effectiveness of treatment.

If a severely affected patient requires major surgical treatment, then safe levels of A.H.G. can be obtained only with animal A.H.G. If surgery can be delayed for 24 hours it is wise to give an initial dose equivalent in potency to 1000–2000 ml. of plasma and to test the rise in A.H.G. level. When giving the first dose, 1 ml. of the solution is given intravenously and if there is no adverse effect after 1 hour the remainder of the dose is given rapidly.

If an initial dose has been given, the size of subsequent doses can be calculated roughly from the effect of the first. Thus if an initial dose equivalent to 2000 ml. of plasma raised the A.H.G. level to 25% of normal, a dose equivalent to 4000–5000 ml. plasma must precede the surgical treatment. If no initial dose was possible then an initial dose equivalent to 5000–7000 ml. should be given to an adult patient.

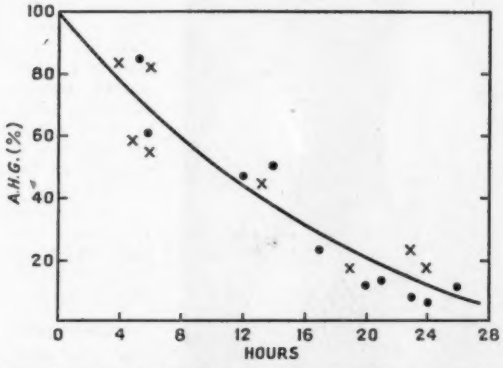


Fig. 2—The curve shows the disappearance of A.H.G. from the blood of treated hæmophilic patients

Points marked X represent results from the blood of patients treated by plasma transfusion. Points marked O represent results from the blood of patients treated with animal A.H.G. In each instance the level of A.H.G. achieved immediately after treatment is taken as 100%. These levels varied in different patients from 25 to 150% of average normal human plasma. The graph is constructed from results obtained with the blood of 12 different patients.

When plasma or A.H.G. is used, the administration of the A.H.G. preparation must be planned to end exactly at the time of the proposed operation. The level of A.H.G. in the patient's blood falls rapidly after administration. The A.H.G. level should always be measured about 15 minutes after the administration of a supposedly active preparation. Should the level fail to rise satisfactorily the patient will probably bleed and the causes for failure, such as inactivity of the preparation or the presence of circulating anticoagulants, can be studied.

Frequency of Dosage

If the level of A.H.G. is followed in the blood of severely affected patients after treatment, it will be found that about half the initial activity is lost in 11 hours and that most of it has disappeared in 24 hours (see fig. 2). Thus to maintain levels above 30% for any length of time is difficult. If one dose of A.H.G. is given daily, the level will be below 30% for much of the time. With present supplies, more frequent dosage is seldom possible. In case 9 of Macfarlane et al. (1957) the level was maintained above 50% for 3 days by slow infusions of extremely large doses of animal A.H.G., equivalent to 13,000, 10,000, and 9000 ml. of fresh plasma. If the operation site can be immobilised so that trauma does not occur at times when the A.H.G. level is low, probably the intermittent daily dose is adequate. Using this method, any procedures which might involve damage to the wound should be timed to take place immediately after a dose of A.H.G.

Duration of Therapy

Treatment should be continued until healing is well advanced. The time will naturally depend on the type of operation performed.

For example multiple dental extractions (which should seldom require animal A.H.G.) may be virtually healed after three daily injections (case 8 of Macfarlane et al. 1957). An operation for the removal of an arteriovenous aneurysm of the brachial artery was healed in 10 days (Fraenkel and Honey 1955), whereas a laminectomy wound was not properly healed in 3 weeks.

The animal A.H.G. used in the operations recorded by Macfarlane et al. (1957) is antigenic and material from one animal (beef or pig) can be used for only about 10 days. Thereafter material from the other animal must be used, and thus the maximum course of treatment is about 3 weeks.

Individual Variations in Response to A.H.G.

At some stage in treatment three patients failed to respond to A.H.G.

Case 8 of Macfarlane et al. (1957) failed to respond to human plasma transfusion. He thereafter responded well to animal A.H.G. for 3 days but then became totally refractory. On admission no circulating anticoagulant could be demonstrated but at the end of his treatment a powerful anticoagulant was present. Presumably the anticoagulant was initially fixed to tissues, and energetic A.H.G. treatment probably stimulated the production of the freely circulating anticoagulant.

The other two cases never had any demonstrable circulating anticoagulant; one of these (recorded by Fraenkel and Honey 1955) was initially resistant to A.H.G. treatment but was found to respond well if the animal A.H.G. was mixed with human plasma. The third case (case 7 of Macfarlane et al. 1957) responded well to two injections of animal A.H.G. but had a marked urticarial reaction after the second dose. He had no response to subsequent doses.

No adequate explanation for the resistance of the last two cases was found.

All but one of the patients studied have required doses of A.H.G. between 2500 and 7000 ml. to raise their blood-A.H.G. level above 30%. Most of the patients who had long-continued treatment showed a progressive decrease in response with the passage of time. This is well shown by figs. 1 and 2 of Macfarlane et al. (1957). One patient

(case 11 of Macfarlane et al. 1957) responded well to small doses of A.H.G., 1000 ml. of plasma raising his blood-A.H.G. level to 70% and correspondingly small doses of animal A.H.G. being effective. There is no known cause for this variability, but the unpredictable response emphasises the need to assay blood-levels of A.H.G. after treatment.

Discussion

The method described here is not exactly the same as that used for the majority of patients recorded by Fraenkel and Honey (1955), Biggs and Macfarlane (1957b), Macfarlane et al. (1957), and Wishart et al. (1957). For most of the studies made in this laboratory the method described by Biggs and Macfarlane (1957a) was used. The present method is proposed because it is thought that it may prove more easily adapted to use in laboratories not especially devoted to work on blood coagulation.

The simple observation of clotting-time and prothrombin consumption on the blood of treated patients unfortunately gives little useful information. The clotting-time may be normal with as little as 1% of A.H.G. in the blood. We customarily observe the clotting-time because the test is simple and quickly performed; if the results are not normal then the treatment has certainly not been effective. The results of A.H.G. assay are usually not available until after the operation is complete, and it is comforting to know that the material has had some effect before the operation is undertaken. The results of the prothrombin-consumption test are seldom restored to normal in the blood of a severely affected hæmophilic patient even when the A.H.G. level is high. Patients have been subjected to surgery with safety even when the results of the prothrombin-consumption test have remained quite abnormal. It appears that the level of A.H.G. is a safer guide to the hæmostatic efficiency of A.H.G. than is the prothrombin-consumption test.

The results of assay method described here have not been correlated with the results of tests described by other workers. It is extremely improbable that methods which differ much in principle (e.g., the method of Wolf 1956) would give precisely the same results.

Although the assay method described is certainly not precise, it has proved of great value in the control of therapy in hæmophilic patients. If surgery has been undertaken when the level of A.H.G., as judged by this method, has been raised to more than 30% of normal, bleeding has been controlled. If for any reason the level has failed to rise above 10–15%, subsequent bleeding has been predicted with irritating reliability.

I should like to thank Miss Ruth Anderson and Miss Sheila Taylor for technical assistance. Dr. R. G. Macfarlane kindly read the typescript.

REFERENCES

Bell, W. N., Alton, H. G. (1955) *Nature, Lond.* **174**, 880.
Biggs, R., Douglas, A. S. (1953) *J. clin. Path.* **6**, 23.
— Eveling, J., Richards, G. (1955) *Brit. J. Hæmat.* **1**, 20.
— Macfarlane, R. G. (1957a) Human Blood Coagulation and its Disorders. Oxford.
— — (1957b) *Brit. J. Hæmat.* (in the press).
Brinkhous, K. M., Langdell, R. D., Penick, G. D., Graham, J. B., Wagner, R. H. (1954) *J. Amer. med. Ass.* **154**, 482.
Fraenkel, G. J., Honey, G. E. (1955) *Lancet*, ii, 1117.
Langdell, R. D., Graham, J. B., Brinkhous, K. M. (1950) *Proc. Soc. exp. Biol., N.Y.* **74**, 424.
— Wagner, R. H., Brinkhous, K. M. (1953) *J. Lab. clin. Med.* **41**, 637.
Macfarlane, R. G., Mallam, P. C., Witts, L. J., Bidwell, E., Biggs, R., Fraenkel, G. J., Honey, G. E., Taylor, K. B. (1957) *Lancet*, ii, 251.
Pitney, W. R. (1956) *Brit. J. Hæmat.* **2**, 250.
Wishart, C., Annand Smith, C., Honey, G. E., Taylor, K. B. (1957) *Lancet*, (in the press).
Wolf, P. (1956) *Brit. J. Hæmat.* **2**, 386.

DEFICIENCY OF AN EXTRA-THYROID ENZYME IN SPORADIC CRETINISM

JAMES H. HUTCHISON
O.B.E., M.D. Glasg., F.R.F.P.S., F.R.C.P.
VISITING PHYSICIAN

GAVIN C. ARNEIL
M.D. Glasg., M.R.C.P., F.R.F.P.S., D.C.H.
UNIVERSITY LECTURER IN CHILD HEALTH

ROYAL HOSPITAL FOR SICK CHILDREN, GLASGOW

E. M. MCGIRR
B.Sc., M.B. Glasg., M.R.C.P., F.R.F.P.S.
UNIVERSITY LECTURER IN MEDICINE, ROYAL INFIRMARY, GLASGOW

IN 1952, a new thyroid hormone, 3 : 5 : 3′-*l*-triiodothyronine, was identified in human plasma (Gross and Pitt-Rivers 1952a). Triiodothyronine, which is also present in the thyroid gland, is much more active than thyroxine (Selenkov and Asper 1955). It is not yet clear whether triiodothyronine in human plasma is formed mainly within the thyroid gland, possibly by the coupling of one molecule of monoiodotyrosine with one molecule of diiodotyrosine (Roche and Michel 1955), or by the partial deiodination of thyroxine in the peripheral tissues (Gross and Pitt-Rivers 1952b). It is probable that both mechanisms operate in the normal individual, because Fellinger et al. (1957) have recently produced evidence to support Roche and Michel's concept of intra-thyroid synthesis of triiodothyronine, whereas Pitt-Rivers et al. (1955) have shown that the thyroxine can be deiodinated to triiodothyronine in the human bereft of the thyroid gland. Both thyroxine and triiodothyronine are carried in the circulation bound to protein, mainly associated with a specific α-globulin, but triiodothyronine is less firmly bound and readily displaced by thyroxine (Deiss et al. 1953). This may explain the relatively low levels of triiodothyronine in the blood, but the absolute amount of this amino-acid, relative to thyroxine, is unknown (Dingledine et al. 1955).

If it is postulated that the peripheral deiodination of thyroxine to triiodothyronine is effected by enzymes, absence or deficiency of such an enzyme might lead to a state of partial hypothyroidism which would not be cured by dry thyroid or *l*-thyroxine but only by triiodothyronine. We report here a case which could be interpreted in such a light.

The patient (right) before treatment. The girl on the left is a normal child of the same age.

Case-report

A girl, aged 4 years and 3 months, was admitted to hospital on April 30, 1954. She was one of heterosexual twins. The birth was uncomplicated and she had then weighed 4½ lb. Her development had always been

EFFECTS OF TREATMENT

—	Before treatment (May 19, 1954)	After 119 days on dry thyroid (Sept. 15, 1954)	After 82 days on triiodothyronine (Dec. 7, 1954)	Last seen (June, 1957)
Height (cm.)	79	83 (+4)	90 (+7)	108 (+18)
Weight (kg.)	12·3	11·6 (−0·7)	14·5 (+2·9)	17·2 (+2·7)
Bone age (yr.)	< 1	< 1	$2^1/_2$	Normal
Behaviour	Sluggish and somnolent	Cross, irritable, and aggressive	Active, animated, coöperative	At school with own age-group. Pleasant child
Speech	Very seldom speaks	Rarely speaks, screams frequently	Speaking freely in intelligible phrases	Speaks well, no deviation from average
Pulse-rate (per minute)	80–100	100–120	90–100	100–110
Facies and hair	Sparse hair, cretinous face	Sparse hair, expressionless hypothyroid facies	Hair growing, features mobile	No abnormality detected

slow. She cut her first tooth at 8 months, walked at 2 years, and did not speak single words until she was 3 years. An umbilical hernia was repaired at 2 years.

She was typically cretinous (see figure) with thick ugly features, large tongue, sparse dry hair, and protuberant abdomen accentuated by lordosis, and she was obviously mentally defective. Her weight was 12·3 kg. (normal 16·1 kg.) and her height 79 cm. (normal 98·6 cm.). Bone age was less than 1 year. Plasma protein-bound ^{127} iodine was 1·8 μg. Radioactive ^{131}I studies (McGirr and Hutchison 1955, case 2) revealed a 24-hour uptake by the thyroid gland of 14% of the dose, and scanning of the neck showed that the only thyroid radio-activity was above the hyoid bone.

Her twin was also mentally retarded but he did not appear to be a cretin. His bone age was normal, and ^{131}I studies gave normal results and showed that the thyroid gland was in the normal site.

Treatment.—Dry thyroid (*B.P.*) (gr. $^1/_4$ daily) was started on May 20, 1954. The dose was rapidly increased to gr. 20 daily by July 3, and subsequently reduced to gr. 5 daily until its withdrawal on Sept. 15. The average daily dose over this 119-day period was gr. $6^1/_2$. While on dry thyroid she changed from a sluggish somnolent state to one of irritability and aggressiveness (see table). She lost 0·7 kg. in weight. Her height increased 4 cm. Her vocabulary did not improve. There was little improvement in her cretinous appearance or in her bone development. Her pulse-rate rose.

On Sept. 16, *l*-triiodothyronine was started in a daily oral dose of 100 μg., which was continued until Dec. 7. During this period of 82 days she improved dramatically. She lost her cretinous features and expressionless facies. She began to speak in sentences. Her weight increased by 2·9 kg., and her height by 7 cm. The bone age increased to $2^1/_2$ years, and the pulse-rate dropped considerably. The improvement in her intellectual responses was very striking but, unfortunately, formal intelligence testing was not done.

On Dec. 7, 1954, the daily dose of triiodothyronine was reduced to 80 μg. daily, and on Sept. 14, 1956, because of tachycardia, tremulousness, and sweating, the dose was further reduced to 40 μg. daily. She is now within the normal range for her age in height and weight. She goes to an ordinary school and is keeping up with her own age-group in class-work. She looks in all respects like a normal child, both mentally and physically.

Comment

It is obvious that this child's cretinous state was not adequately reversed by dry thyroid, whereas triiodothyronine produced dramatic improvement and has maintained the child in normal mental and physical health. If we assume that there was a failure of deiodination of thyroxine to triiodothyronine in this patient, it follows that she had available for metabolism by her receptor cells only the small quantities of triiodothyronine which could be produced by her inadequate sublingual thyroid remnant. This hypothesis would be compatible with her cretinous state, which was never as severe as that seen in cretinism due to congenital athyreosis, in which the uptake of ^{131}I by the thyroid gland is virtually nil (McGirr and Hutchison 1955). It could also explain the failure in treatment with dry thyroid and the success with triiodothyronine. In recent years, non-endemic goitrous cretinism, often familial, has been attributed to an inborn deficiency of one of various specific enzymes within the thyroid gland (Stanbury et al. 1955, 1956, Hutchison and McGirr 1956, McGirr et al. 1956). If intra-thyroid enzymes can be deficient it seems rational to look for an occasional case of inborn deficiency of an extra-thyroid enzyme concerned with the deiodination of thyroxine to triiodothyronine. We suggest that the hypothyroid state of our patient may represent the results of such a deficiency, which, so far as we are aware, has not previously been recorded.

Summary

A child with non-goitrous sporadic cretinism failed to respond adequately to dry thyroid, but the abnormalities were completely reversed by *l*-triiodothyronine.

It is postulated that in this patient there was an inborn deficiency of an enzyme concerned in the peripheral extra-thyroid deiodination of thyroxine to triiodothyronine.

We are indebted to Prof. Stanley Graham for permission to study this patient, who was under his care. Triiodothyronine was supplied by Glaxo Laboratories Ltd.

REFERENCES

Deiss, W. P., Albright, E. C., Larson, F. C. (1953) *Proc. Soc. exp. Biol., N.Y.* **84**, 513.
Dingledine, W. S., Pitt-Rivers, R., Stanbury, J. B. (1955) *J. clin. Endocrin.* **15**, 724.
Fellinger, K., Höfer, R., Vetter, H. (1957) *Ibid*, **17**, 483.
Gross, J., Pitt-Rivers, R. (1952a) *Lancet*, i, 439.
— — (1952b) *Ibid*, p. 593.
Hutchison, J. H., McGirr, E. M. (1956) *Ibid*, i, 1035.
McGirr, E. M., Hutchison, J. H. (1955) *J. clin. Endocrin.* **15**, 668.
— — Clement, W. E. (1956) *Lancet*, ii, 906.
Pitt-Rivers, R., Stanbury, J. B., Rapp, B. (1955) *J. clin. Endocrin.* **15**, 616.
Roche, J., Michel, R. (1955) *Physiol. Rev.* **35**, 583.
Selenkov, H. A., Asper, S. P. (1955) *J. clin. Endocrin.* **15**, 285.
Stanbury, J. B., Meijer, J. W. A., Kassenaar, A. A. H. (1956) *Ibid*, **16**, 848.
— Ohela, K., Pitt-Rivers, R. (1955) *Ibid*, **15**, 54.

"It is right and proper that a scientific worker should always feel free to express his ideas and formulate his hypotheses, so that they may be available not only to himself but also to his fellow workers. Naturally there may be a reluctance to do this (particularly in the case of younger scientists) lest the hypotheses should later prove to be faulty. But every scientist is entitled to offer an interpretation of his observations, even if it can only be a provisional one, without running the risk of being discredited as a scientist because subsequent investigations replace it by an alternative interpretation. It may be that in some fields of science progress would be more rapid than it is if the workers in those fields were not inhibited in the free expression of their ideas by fears for their scientific prestige. If this should really be so, the more's the pity, for the advancement of science is more important than the advancement of the scientist and, in any case, no scientist should be penalized in his career because he is not consistently right."—Sir WILFRID LE GROS CLARK, F.R.C.S., F.R.S., in Lectures on the Scientific Basis of Medicine. London, 1957; vol. 5, p. 17.

UNNECESSARY IRRADIATION IN CHEST RADIOGRAPHY

W. G. CLARKE

RADIOGRAPHER, MEDICAL RESEARCH COUNCIL'S PNEUMOCONIOSIS RESEARCH UNIT, LLANDOUGH HOSPITAL, PENARTH, GLAMORGAN, WALES

Osborn (1956) states that chest films make up about 20% of all diagnostic radiological examinations but contribute only 0·1% of the genetically significant radiation in the male and even less in the female. The genetically significant radiation was computed from figures of Stanford and Vance (1955) for one hospital "where particular care is taken to reduce the gonad dose to the minimum." The average dose for the male for a full-sized chest film was 0·36 mr.

How representative this figure is of the dose during routine chest radiography up and down the country, including mass-radiography units, is at present unknown; but during investigations into the dose of radiation to the skin and gonads in a number of radiographic units I was impressed by the unnecessary radiation a patient often receives when using the standard cones as supplied by the makers.

The three photographs A, B, and C (fig. 1)* were taken using the same factors (60 in. focal film distance, 65 kV, 30 mA) and the three different-sized diaphragms shown at the bottom right-hand corner of the pictures. 1A and B are the diaphragms supplied to many departments by the makers of the sets. Figs. 1A and B show the large area outside the chest exposed to primary radiation. The doses shown (see table) were measured with an ionisation chamber at varying levels from the top of the head. With the largest cone ($2^1/_2$ in. diameter) the whole of the arms, the abdomen, and much of the pelvis are included in the direct radiation. These measurements were made on a patient of a height of $63^1/_2$ in.; with shorter patients and children the abdominal and gonad doses would be greater and with antenatal patients the uterus and fœtus would be within the area of primary radiation. The great improvement demonstrated in fig. 1C can be obtained by the simple expedient of inserting a sheet of lead 1 mm. thick, with a 1·5 in. square hole in its centre, at the base of the cone.† With this modification the gonad dose can be reduced to one-

SUMMARY OF FINDINGS

Size of diaphragm	Ratio of skin area irradiated	Gonadal dose (male) (mr)	Dose (mr) at various distances from top of head				
			12 in.	18 in.	22 in.	24 in.	26 in.
A, $2^1/_2$ in. circle	2	0·7	100	126	124	124	100
B, 2 in. circle ..	1·5	0·3	100	126	120	110	7·0
C, $1^1/_2$ in. square	1	0·1	90	126	60	4	1·5

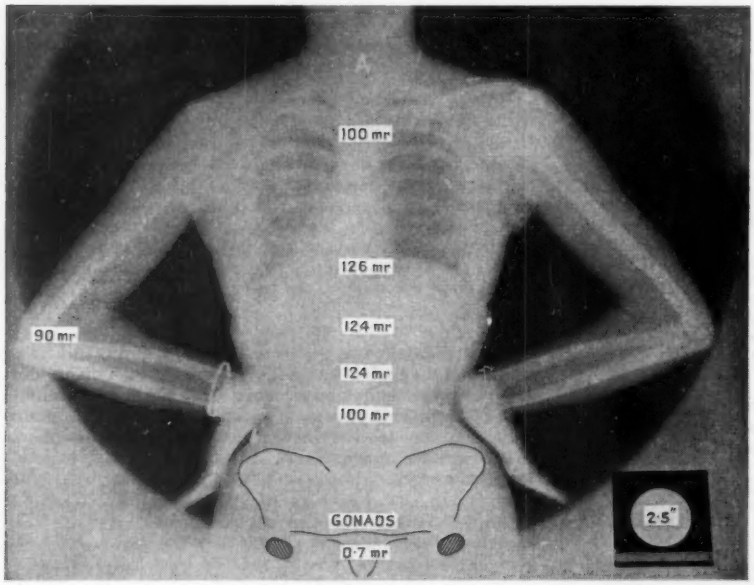


Fig. 1A.

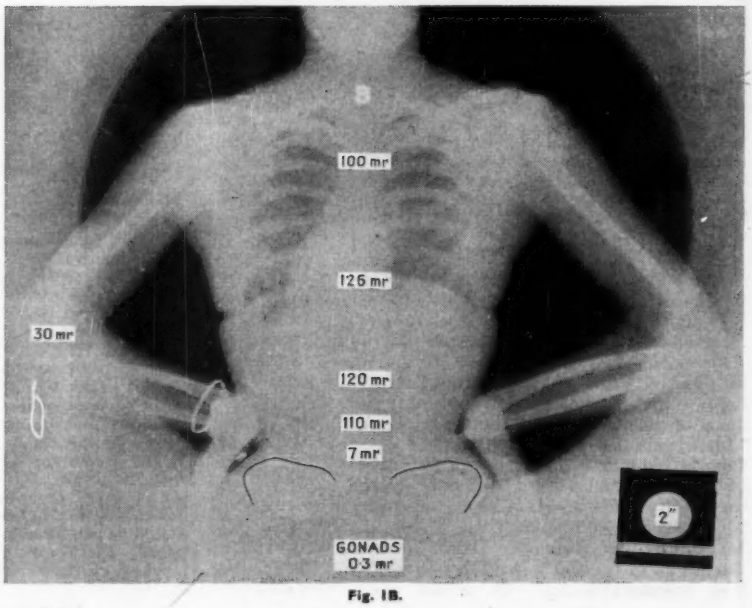


Fig. 1B.

* Copies of the photographs are available for use in teaching centres. Application should be made to the author.

† Messrs. Otley Rhodes, Newport, are prepared to carry out modification of diaphragms.

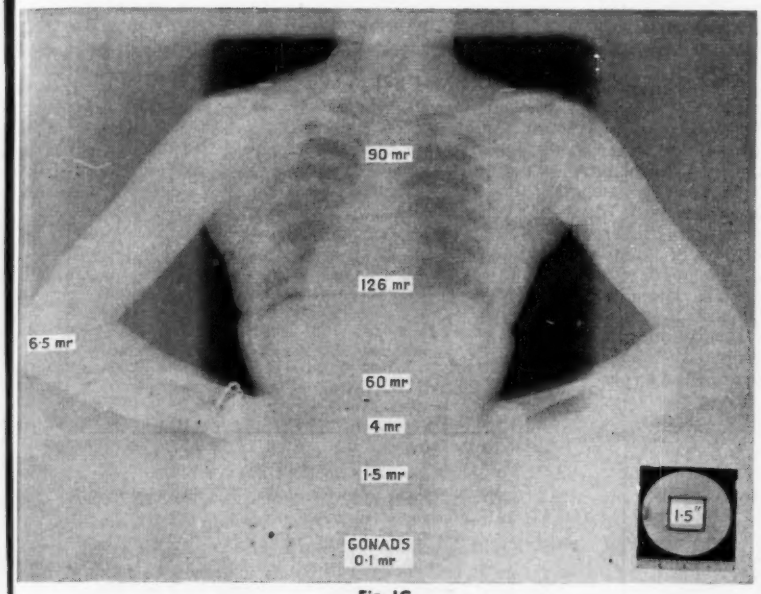


Fig. 1C.

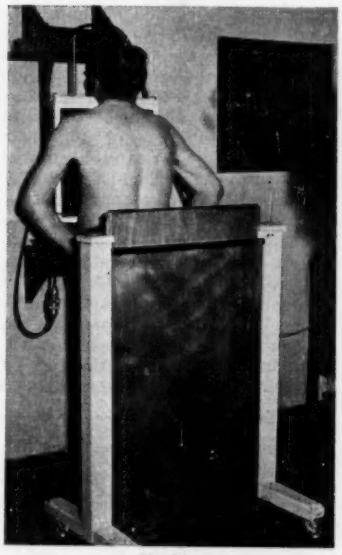


Fig. 2A.

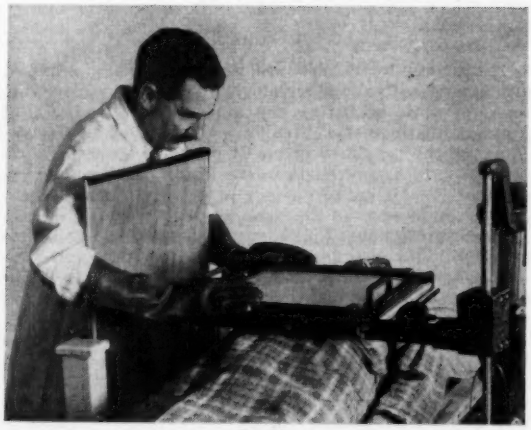


Fig. 2B.

seventh and the skin dose due to primary radiation reduced to a half compared to the large cone, and some further improvement still might be expected from using the extra screening recommended by Ardran (1956).

Figs. 2A and B show an adjustable screen made of two sheets of lead-ply (total shield equivalent, 1 mm. lead), which has many uses in a radiographic department both for reducing still further the gonad dose during chest and other radiography and for protecting an operator during screening. The lead-ply is counterbalanced by weights in the supporting pillars, as in a sash window.

Summary

Bromide paper (3 × 3 ft.) coated with X-ray emulsion has been used to demonstrate the effect of cone size and shape on the area of the body exposed to primary radiation during routine chest radiography. A $1^1/_2$ in. square diaphragm at the base of the cone reduces the gonad radiation in the male to about one-seventh (0·1 mr) of that received when using the standard $2^1/_2$ in. circular diaphragm, and it halves the direct skin radiation. An easily movable protective screen is described for general use in radiographic departments.

I am grateful to Dr. R. G. Wood and Mr. W. Sutherland who were responsible for the radiation measurements. I would also like to thank Mr. J. Chambers and Miss S. Latham for their work in preparing the illustrations and Messrs. Kodak Ltd. for supplying the bromide paper.

REFERENCES

Ardran, G. M. (1956) *Brit.J. Radiol.* **29**, 266.
Osborn, S. B. (1956) Appendix K. Hazards to Man of Nuclear and Allied Radiations. H.M. Stationery Office.
Stanford, R. W., Vance, J. (1955) *Brit. J. Radiol.* **28**, 266.

EFFECTS OF CERTAIN PROTEIN FOODS ON BLOOD-SUGAR LEVELS AND GLUCOSE TOLERANCE

M. SRINIVASAN
D.Sc. Madras, F.R.I.C.
ASSISTANT DIRECTOR, DIVISION OF BIOCHEMISTRY AND NUTRITION, CENTRAL FOOD TECHNOLOGICAL RESEARCH INSTITUTE, MYSORE

MORE than a year ago, it was casually observed that a diabetic patient requiring 20 units of insulin ceased to have glycosuria for the three months during which his food included about 4 to 6 oz. a day of tender field-beans (*Dolichos lablab*).[1] During this period, he took a minimum of fat but liberal quantities of carbohydrate (rice) and had no insulin; yet, surprisingly enough, his fasting blood-sugar level and postprandial peak had become almost normal. Unlike the tender seeds, the mature dolichos had less effect. It was found, again fortuitously, that he derived similar benefits from *idli* [2] diet, or diets

1. This legume, a pulse, is raised by dry farming, and the pods are ready during September–February every year. The tender seed of this pod is cooked and consumed as a seasonal vegetable, especially in the southern State of Mysore.
2. A steam-cooked preparation made from the fermented dough of black gram (*Phaseolus mungo*, another legume pulse, otherwise called *Urud*), and rice, in the approximate proportions of 1 : 2 (by weight). *Idli* is a common article of tiffin in many South Indian homes and restaurants, and its use is gradually spreading to other parts of India.

containing a lot of skim-milk powder. It was found later that in certain other hyperglycæmic patients, who had been advised to take these protein foods, glycosuria diminished; but the response varied in degree.

As a first step towards understanding the cause of these changes we have determined the effects on blood-sugar levels and glucose tolerance of ingesting known quantities of these protein foods and their proteins.[3] Experiments were carried out with this limited object in 3 hyperglycæmic men (A, B, and C) and two healthy men (D and E). For comparison, the effects were studied of ingesting red gram (*Cajanus cajan*, also a legume pulse, and called *Thur dahl*), gelatin, and a mixture of amino-acids, as in casein; and, in one subject (A) the effect of 20 units of plain insulin given subcutaneously immediately after glucose was also recorded. The dose of glucose was kept constant for each subject throughout the experiments, at the rate of about 1 g. per kg. body-weight. The inherent causes of the high blood-sugar in the hyperglycæmic patients were not studied.

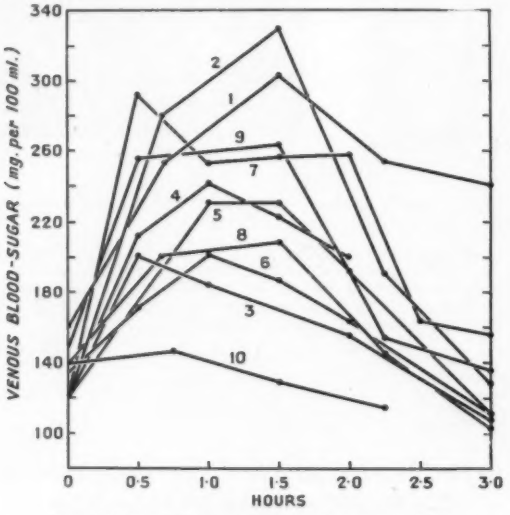


Fig. 1—Glucose-tolerance curves: A, a man aged 48.

(1) 75 g. glucose in 150 ml. water.
(2) 75 g. glucose in 150 ml. water, followed immediately by 20 units plain insulin subcutaneously.
(3) Casein ('B.D.H. Light white, soluble') equivalent to 30 g. protein, suspended in water and ingested together with 75 g. glucose.
(4) Amino-acids (chemically pure) as in 45 g. casein; added to 75 g. glucose in solution and ingested.
(5) Gelatin ('Difco'): 40 g. in water and ingested together with 75 g. glucose.
(6) Protein from *tender* seeds of *Dolichos lablab*: 45 g. pressure-cooked (10 lb. per square in. for 30 min.) and ingested: 75 g. glucose given $2^1/_2$ hr. later.
(7) Protein from *mature* seeds of *Dolichos lablab*: 45 g. pressure-cooked as above and ingested: 75 g. glucose given $2^1/_2$ hr. later.
(8) 50 g. *Phaseolus mungo* (black gram *dhal*, dehusked), soaked overnight, cooked in the same water and ingested: 75 g. glucose given 1 hr. later.
(9) 50 g. *Cajanus cajan* (*Thur dhal*, dehusked): cooked and ingested: 75 g. glucose given 1 hr. later.
(10) As (8), but without glucose.
(All were given by mouth.)

3. Estimation of blood-sugar levels: venous blood was drawn into test-tubes containing fluoride and oxalate, and deproteinised by copper sulphate-sodium tungstate (Somogyi 1931), sugar in the filtrate was estimated by alkaline copper (Somogyi 1952) arsenomolybdate (Nelson 1944) method. The colour of the test solution and that of the standard were read against the blank in the Klett-Summerson colorimeter, using filter KS 620.

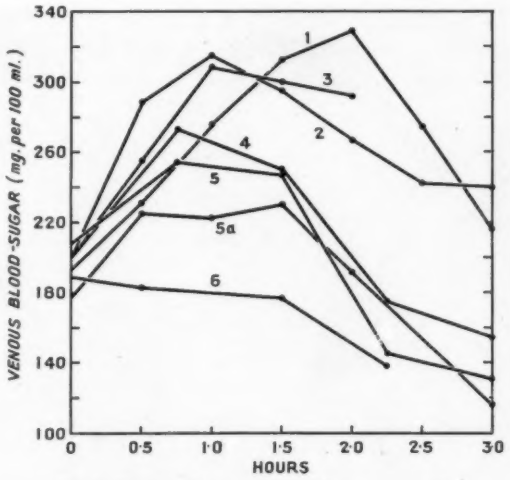


Fig. 2—Glucose-tolerance curves: B, a man aged 52.

(1) 75 g. glucose in 150 ml. water.
(2) 30 g. casein and 75 g. glucose together.
(3) 60 g. casein; $2^1/_2$ hr. later, 75 g. glucose.
(4) 50 g. *Thur dhal*; 1 hr. later, 75 g. glucose.
(5) 50 g. black gram *dhal*; 1 hr. later 75 g. glucose.
(5a) 100 g. black gram *dhal*; 1 hr. later 75 g. glucose.
(6) As (5), but without glucose.

Results

The glucose-tolerance curve, in both normal and hyperglycæmic subjects, was significantly altered by ingesting, together with or before the glucose, certain types of proteins (distinguished here only on the basis of source). Thus, at the arbitrary levels of protein ingested, casein (fig. 1, curve 3, and fig. 4, curve 2), protein from *tender* dolichos (fig. 1, curve 6), and protein from black gram (fig. 3, curve 5) gave the most striking results. Protein from *mature* dolichos (fig. 1, curve 7) was found to be less effective. This accords with the finding that the ameliorative effect of dolichos on glycosuria decreased with the maturity of the seed. Gelatin was found less effective than casein (fig. 1, curve 5).

Like the proteins, the corresponding protein-bearing foodstuffs were found to be effective. Thus, it is significant from the viewpoint of practical dietetics that when subject B was fed 100 g. black gram—i.e., 20 g. protein and 60 g. carbohydrate, which is the average composition of a legume (Patwardhan and Ranganathan 1956)—and an hour later 75 g. glucose, a low peak was registered (fig. 2, curve 5a) and a final blood-sugar of only 118 mg. per 100 ml. (average fasting level 195 mg.). The lowering in peak seems to be related to the quantity of protein ingested (compare fig. 2, curve 5, with fig. 2, curve 5a). Black gram kept down the blood-sugar (fig. 1, curve 10, fig. 2, curve 6, fig. 4, curve 5) and increased the tolerance to glucose (fig. 1, curve 8, fig. 4, curves 4 and 7). Subject C, who responded favourably to 45 g. protein isolated from black gram (fig. 3, curve 5), did not respond to 20 g. protein provided by 100 g. black gram (fig. 3, curve 2). The minimum individual protein requirement has to be determined, and will probably be found to bear a linear relationship to the extent of hyperglycæmia in a frank case.

Red gram (*Thur dhal*) (fig. 1, curve 9, fig. 2, curve 4, and fig. 4, curve 3) usually had less effect on tolerance to sugar than black gram (fig. 1, curve 8, fig. 2, curve 5, fig. 4, curve 4). But with subject E, red gram (fig. 4, curve 8) was more effective than black gram (fig. 4, curve 7). This healthy man of 23 (the youngest of our subjects) appeared exceptional in other respects too.

Thus, during the glucose-tolerance test, with or without protein, he repeatedly had a very low blood-sugar level about $2^1/_4$ hours after glucose (fig. 4, curve 6), the curve then turning upwards towards normal. But at this low level of blood-sugar he had no hypoglycæmic symptoms. No explanation can yet be offered for the repeatable abnormal behaviour of this subject. Venous blood-sugar levels far lower than the initial fasting level have been recorded in glucose-tolerance tests in young adults—sometimes with hypoglycæmic effects (Peters and Van Slyke 1946).

Some other apparent discrepancies in the results were :

(1) The unresponsiveness of the hyperglycæmic patient B to casein at either dose (fig. 2, curves 2 and 3). Barone and Costa (1931) have likewise reported inconsistent results on the effects of casein in diabetic patients.

(2) The difference in the effectiveness of the protein of tender dolichos on the glucose tolerance between the hyperglycæmic patients A (fig. 1, curve 6) and C (fig. 3, curve 3).

(3) The necessity, in the patient C, of giving black gram protein along with glucose (fig. 3, curve 5), rather than $2^1/_2$ hours before it (fig. 3, curve 4), for him to derive the maximum effect from this protein.

Possible Mechanisms

Protein Altering the Rate of Absorption of Glucose.—This is probably not the mechanism since :

(1) Not all the proteins tried had the same result in a given subject (fig. 1), nor did one protein give similar results with every subject (e.g., casein in patients A and B).

(2) The peak in blood-sugar was reached within $^1/_2$–1 hour after the glucose was given, and then there was a sharp decline in the curve. One would not expect this if glucose was being slowly absorbed and released into the blood-stream.

(3) Within this short period, the protein could not have reached the site of glucose-absorption (small intestine).

Effect of Protein Fragments.—If the protein could not reach the small intestine in time, it would be even less likely to have split into amino-acids. That these are not implicated is further borne out by smaller effect of a mixture of amino-acids equivalent in composition to the test-dose of casein in 1·5 times the quantity (fig. 1, curve 4). The involvement of polypeptides or lower protein fragments is more plausible. Mellinkoff et al. (1956) report

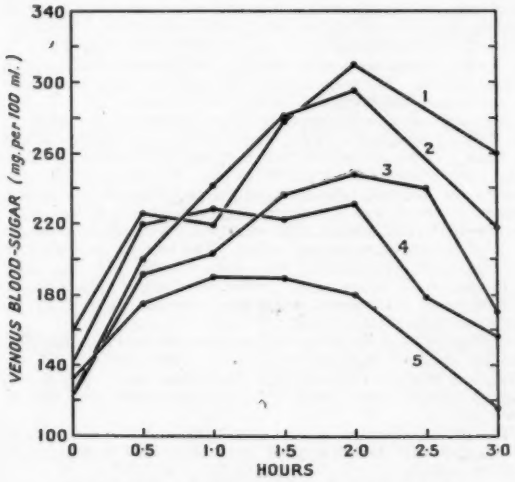


Fig. 3—Glucose-tolerance curves : C, a man aged 44.

(1) 75 g. glucose in 150 ml. water.
(2) 100 g. black gram *dhal* and 75 g. glucose together.
(3) 45 g. protein from tender seeds of *Dolichos lablab* ; $2^1/_2$ hr. later, 75 g. glucose.
(4) 45 g. protein from black gram ; $2^1/_2$ hr. later, 75 g. glucose.
(5) As (4), but protein and glucose ingested together.

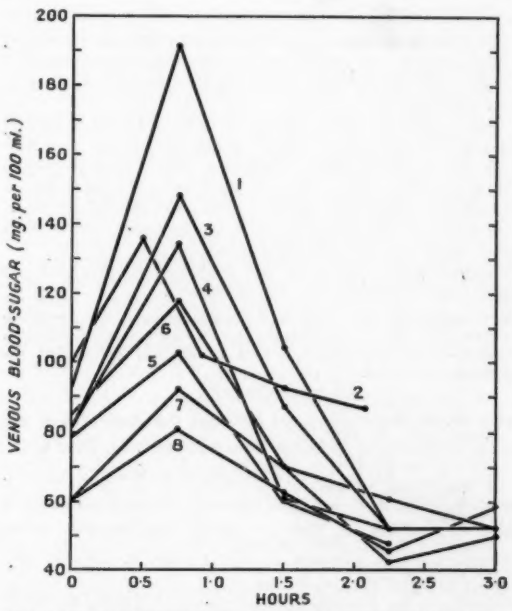


Fig. 4—Glucose-tolerance curves. Nos. 1–5 : D, a man aged 32. Nos. 6–8 E, a man aged 23.

(1) 75 g. glucose in 150 ml. water.
(2) 30 g. casein and 75 g. glucose together.
(3) 50 g. *Thur dhal* ; 1 hr. later, 75 g. glucose.
(4) 50 g. black gram *dhal* ; 1 hr. later, 75 g. glucose.
(5) 50 g. black gram *dhal* only.
(6) 60 g. glucose in 120 ml. water.
(7) 50 g. black gram *dhal* ; 1 hr. later, 60 g. glucose.
(8) 50 g. *Thur dhal* ; 1 hr. later, 60 g. glucose.

that ingestion of hydrolysed casein causes a fall in blood-sugar in experimental subjects. A preliminary experiment has shown that glucose administered with the enzyme-digest of tender dolichos (the clear supernatant solution obtained after incubating the seed homogenate overnight) produced no glycosuria in a hyperglycæmic patient in 3 hours, whereas, when glucose was given alone, glycosuria was evident. We are studying the effect on blood-sugar and glucose tolerance of ingesting proteins hydrolysed in various degrees by enzymes.

Discussion

The reduction of the blood-sugar by protein after ingestion of carbohydrate was first demonstrated by Cochrane et al. (1956). The experiments now reported show another facet of this hitherto neglected function of protein. The reporting of these results, incomplete as they are, seems, therefore, to be warranted at this stage. Reports have been conflicting on the effects of ingesting proteins (or protein hydrolysates) on blood-sugar (Jacobson and Edwards 1920, Ciaccio and Racchiusa 1926, Glatzel 1929, Overgaard 1929, Hamel et al. 1935, Vartiainen and Apaljalahti 1955). The lack of agreement seems to stem from differences in the type of protein used. A systematic study of the effects of protein on blood-sugar levels is called for.

The possibility of using glucose and an effective protein as a diet for the hyperglycæmic patient needs to be kept in view. Many reports have appeared on oral antidiabetic compounds (Lewis 1949). It is obvious that if improvement could be obtained merely by qualitative (not quantitative) control of feeding, using composite foods based on certain types of proteins, this would be a better method of control than drugs which might have ill effects.

Summary

The effects on blood-sugar levels and glucose tolerance of ingesting known quantities of certain protein foods and proteins have been determined in 3 hyperglycæmic men and 2 healthy men.

Casein, protein from tender dolichos (*Dolichos lablab*) and protein from black gram (*Phaseolus mungo*), as also black gram itself, were effective. *Thur dhal* (*Cajanus cajan*), protein from mature dolichos, gelatin, and a mixture of amino-acids as in casein were less effective.

In addition to variation due to proteins, the effects varied with the individuals studied.

Possible mechanisms for the observed effects, and the significance of the results, are discussed.

My thanks are due to Dr. V. Subrahmanyan, director of the nstitute, for his kind interest; to the subjects who volunteered for the experiment; and to several colleagues for technical assistance.

REFERENCES

Barone, V. G., Costa, A. (1931) *Boll. Soc. ital. Biol. sper.* **6**, 24; *Chem. Abstr.* **25**, 3037.
Ciaccio, C., Racchiusa, S. (1926) *Boll. Soc. ital. Biol. sper.* **1**, 51; *Chem. Abstr.* **22**, 1794.
Cochrane, W. A., Payne, W. W., Simpkiss, M. J., Woolf, L. I. (1956) *J. clin. Invest.* **35**, 411.
Glatzel, H. (1929) *Arch. exp. Path. Pharmak.* **143**, 234; *Chem. Abstr.* **24**, 2161.
Hamel, J., Chavarot, M., Aubry, P. (1935) *C.R. Soc. Biol. Paris*, **119**, 864; *Chem. Abstr.* **29**, 6928.
Jacobson, A. Th.B., Edwards, H. (1920) *Amer. J. med. Sci.* **159**, 833; *Chem. Abstr.* **15**, 876.
Lewis, J. J. (1949) *Physiol. Rev.* **29**, 75.
Mellinkoff, S. M., Frankland, M., Boyle, D., Greipel, M. (1956) *J. appl. Physiol.* **8**, 535; *Chem. Abstr.* **50**, 14066.
Nelson, N. (1944) *J. biol. Chem.* **153**, 375.
Overgaard, K. (1929) *Hospitalstidende*, **72**, 1241; *J. Amer. med. Ass.* **94**, 1108; *Chem. Abstr.* **24**, 4866.
Patwardhan, V. N., Ranganathan, S. (1956) Health Bulletin, no. 23, Coonoor. New Delhi. p. 30.
Peters, J. P., Van Slyke, D. D. (1946) Quantitative Clinical Chemistry. Interpretations. Baltimore; vol. I, pp. 168–9.
Somogyi, M. (1931) *J. Biol. Chem.* **90**, 725.
— (1952) *Ibid*, **195**, 19.
Vartiainen, I., Apaljalahti, J. (1955) *Ann. Med. intern. Fenn.* **44**, 95; *Chem. Abstr.* **50**, 5905.

PRIMARY HYPEROXALURIA

H. E. ARCHER
M.R.C.S., F.P.S., F.R.I.C.
CONSULTANT CHEMICAL PATHOLOGIST

A. E. DORMER
M.D. Lond., M.R.C.P.
SENIOR REGISTRAR

E. F. SCOWEN
M.D. Lond., F.R.C.P.
DIRECTOR OF THE MEDICAL UNIT

R. W. E. WATTS
M.B., Ph.D. Lond., M.R.C.P.
SENIOR LECTURER IN MEDICINE

ST. BARTHOLOMEW'S HOSPITAL, LONDON

A FEW cases have been reported in which renal calculus formation, nephrocalcinosis, and the deposition of calcium oxalate in the extrarenal tissues have been thought to be associated with an abnormally high urinary excretion of oxalate. The high excretion, however, has been demonstrated by chemical measurement in only three cases (Newns and Black 1953, Aponte and Fetter 1954). The literature up to 1955 was reviewed by Dunn (1955), since when further cases have been added by Lund and Reske-Nielsen (1956) and by Lund (1957).

We report here, two cases in which the diagnosis was confirmed chemically, and indicate the natural history of the condition. A metabolic error which may be responsible is suggested.

Case-reports

Case 1.—A boy born in 1933 presented with hæmaturia and the passage of multiple small urinary stones at the age of 1 year, when small calculi were demonstrated radiologically in both renal pelves. At the age of 3 two calculi of unknown chemical composition were removed from the left renal pelvis, and two were removed from the bladder; these operations were complicated by suppression of urine and a urinary infection respectively. When he was 4 another two stones composed mainly of calcium oxalate were removed from the right renal pelvis. Four months after this operation calcium-oxalate crystals and an excessive number of leucocytes were found in his urine, his right kidney was hydronephrotic, and stones had reformed in his left renal pelvis. The latter were removed and the left pelviureteric junction reconstructed.

TABLE I—URINARY EXCRETION OF OXALATE IN TWO CASES OF PRIMARY HYPEROXALURIA

Case 1		Case 2	
Date	Urinary oxalate (mg. of $(COOH)_2.2H_2O$ per 24 hr.)	Date	Urinary oxalate (mg. of $(COOH)_2.2H_2O$ per 24 hr.)
July, 1955	162	January, 1955	240
June, 1956	183–242 (13)*	April, 1955	110–165 (15)
September, 1956	169–225 (12)	February, 1956	115–174 (16)
November, 1956	236	October, 1956	242
January, 1957	242	December, 1956	265
March, 1957	290	January, 1957	160
		March, 1957	167

* The numbers in parentheses indicate the number of observations (i.e., consecutive 24-hour urine collections) on which the quoted range of values is based.

The patient was admitted twice to other hospitals between 1938 and 1946 with symptoms referable to urinary calculi, and underwent a further operation, of uncertain nature, on his urinary tract.

A staphylococcal urinary infection followed cystolithotomy in February, 1946, and this was not finally eradicated (by intensive penicillin therapy) till October, 1947. At this time both his kidneys concentrated radio-opaque contrast medium poorly, bilateral renal calculi and hydronephrotic changes were apparent, and the number of calculi had obviously increased since February, 1946.

In 1951, at the age of 16, the boy had part of his left kidney excised. This operation was followed by a temporary disturbance of electrolytes and increased azotæmia (the highest blood-urea level recorded being 237 mg. per 100 ml.). Histologically, the excised tissue showed only the effects of pyelonephritis. The blood-pressure was then 150/110 mm. Hg.

The amount of oxalate in his urine was first measured in 1955 (table I). At that time the urine was sterile but contained protein, many erythrocytes, and a few leucocytes. In June, 1956, he was admitted at the age of 21 with aching pains in both loins, hæmaturia after exercise, and passing small calculi per urethram. He passed about 2·5 litres of urine daily, and nocturia had just begun.

Investigations, additional to those recorded in table II, showed: hæmoglobin 13·9 g. per 100 ml., and serum-sodium 330 mg., serum-potassium 18·0 mg., serum-chloride 580 mg., and blood-uric acid 3·8 mg. per 100 ml. Plasma-proteins were 7·4 g. per 100 ml. (albumin 5·3 g., globulin 2·1 g.) with a normal pattern on filter-paper electrophoresis. A fractional test-meal showed normal acid secretion. Urea-clearance was 32% of the average normal value. The urinary excretion of calcium and phosphorus was respectively 147 mg. and 1140 mg. in 24 hours on an unrestricted diet. The urinary excretion of free amino-acids was normal, as judged by filter-paper chromatography.

Radiography of the whole skeleton revealed no abnormality, but the amount of renal calcification, especially on the left side, had increased during the preceding year. Mr. L. G. Fison reported that there were no crystalline deposits in the eyes.

The patient has one brother (aged 21), and there is nothing to suggest that he or any of the other near relations has urinary calculi.

Case 2.—A girl born in 1947 presented at the age of 4 years with renal pain and hæmaturia of recent onset, there having been no previous symptoms suggesting disease of her urinary tract. A left renal calculus was detected at this time and was removed in 1952. In October, 1953, after two further episodes of frank hæmaturia, radiography revealed calculi in the right upper calyces and the left renal pelvis; the urine contained many calcium-oxalate crystals, a few erythro-

cytes and leucocytes, and was sterile. The urea-clearance was 48·4% of the average normal value. An almost pure calcium-oxalate stone was removed from the left renal pelvis, and tissue weighing 10 g. was excised from the upper pole of the right kidney together with a calcium-oxalate stone. The histological report by Dr. R. J. R. Cureton on the excised kidney tissue was as follows: "Little destruction of cortex and medulla. There is some slight focal scarring affecting the cortex, and in these areas there is some chronic inflammatory infiltration together with some polymorphonuclear leucocytes. The increased intertubular connective tissue contains occasional masses of crystalline material staining positively by van Kossa's method, but most of this is present in the second convoluted tubules, particularly in those limbs adjacent to glomeruli. Some of the crystalline masses have a dumb-bell shape, and some are covered by regenerated epithelium. Very little crystalline material is seen in the medulla. The blood-vessels show no gross pathological change."

The urinary excretion of oxalate was measured first in 1954 (table I) and again in 1955, daily measurements being made over about three months, and it was shown that neither a cane-sugar-free diet (administered for 33 consecutive days) nor a low-protein diet (administered for 5 consecutive days) influenced the amount of oxalate excreted in the urine.

In February, 1956, when she was 9, the child was readmitted for more detailed investigation. At this time her height was 4 ft. 3 in., her weight 4 st. 6 lb., and her blood-pressure 120/80 mm. Hg. She had no symptoms, and her urine was sterile, although microscopic hæmaturia was present and the calculi in both renal pelves had increased in size.

Investigations additional to those recorded in table II showed hæmoglobin 14·1 g. per 100 ml., red cells 4,600,000 per c.mm.; and leucocytes 6100 per c.mm. (differential count normal). The erythrocyte-sedimentation rate was 4 mm. in 1 hour (Westergren). Serum-sodium was 330 mg., serum-potassium 15·0 mg., serum-chloride 560 mg., and blood-uric acid 5·2 mg. per 100 ml. A fractional test-meal showed normal acid secretion. Urea-clearance was 62·5% of the average normal value. The urinary excretion of calcium was 133 mg. in 24 hours on a diet of unrestricted calcium content. The urinary excretion of free amino-acids was normal as judged by filter-paper chromatography.

Radiography of the whole skeleton revealed no abnormality, and Mr. J. H. Dobree reported that there were no crystalline deposits in the eyes.

There is no history suggesting urolithiasis in this patient's three siblings (aged 2, 7, and 11 years) or in her other near relations.

Representative blood-pressure readings and the results of routine biochemical tests on these patients over the years are presented in table II.

Amount of Oxalate Excreted

The urinary oxalate was determined by the procedure described by Archer, Dormer, Scowen, and Watts (1957), except that 0·1 *N* $KMnO_4$ was used instead of 0·01 *N* $KMnO_4$ for the final titration.

The urine was filtered quickly through a coarse filter-paper (Green's no. 904½), while still warm, the filtrate being collected in a bottle containing concentrated HCl (5 ml. acid per litre of urine). It is important that urine samples should not be allowed to cool before being added to the main 24-hour collection, because gross errors may arise from the crystallisation of calcium oxalate in bedpans and urinals.

Table I shows the urinary excretion of oxalate over about 2 years. The patients took an unrestricted diet except that foods known to be especially rich in oxalate—e.g., rhubarb, spinach, strawberries, cocoa, and chocolate—were excluded when the determinations were performed. The normal urinary excretion of oxalate determined by this method is equivalent to about 10–40 mg. $(COOH)_2.2H_2O$ in 24 hours (Archer et al. 1957).

TABLE II—BLOOD-PRESSURE AND BLOOD CHEMISTRY IN TWO CASES OF PRIMARY HYPEROXALURIA

Case (no.)	Age (yr.)	Blood-pressure (mm. Hg)	Blood chemistry				
			Blood-urea (mg. per 100 ml.)	Serum-inorganic phosphate (mg. per 100 ml.)	Serum-calcium (mg. per 100 ml.)	Plasma alkali reserve (vol. CO_2 per 100 ml.)	Serum-alkaline phosphatase (King-Armstrong units per 100 ml.)
1	4	110 (systolic)	45	3·0	11·2	54·8	..
	11	130/70	..	..	9·8	..	..
	12	125/90	45	3·4	..	59·5	10·6
	16	150/110	50*	..	..	..	..
	20	150/110	52	4·1–4·5†	11·1–11·7†	41·4	9·0–9·5
	21	145/110	62	3·5	11·3	57·6	..
2	4	..	36	5·3	10·6	..	9·4
	8	..	33	4·8	10·8–11·7†	52·0	14·0
	9	120/80	43	4·9	9·6	48·1	..
	11	130/80	20	..	..	57·6	..

* Preoperative value (see text).
† Range of three separate determinations during this admission.

Discussion

The term "oxaluria" is generally used to denote increased urinary excretion of oxalate from any cause (Hawk et al. 1949), and, since the urinary oxalate is rarely measured, the diagnosis is usually made on the presence of calcium-oxalate crystals "in more than average numbers" in centrifugal urinary deposits. As urine normally contains a small amount of oxalate, we suggest that the term "hyperoxaluria" should be used where an abnormally high urinary excretion of oxalate can be demonstrated chemically, and that cases such as we have reported here should be described as having "primary hyperoxaluria." Transient increases in the urinary excretion of oxalate after the ingestion of very large amounts of diffusible oxalate (Barrett 1942, Archer et al. 1957) could then be labelled "secondary hyperoxaluria." The formation of disseminated extrarenal calcium-oxalate deposits produces a condition which is conveniently called "oxalosis" (Dunn 1955).

Primary hyperoxaluria appears to be rare, for only twenty-six patients under the age of 15 years suffering from renal calculi are recorded as having been admitted to teaching hospitals contributing to the Registrar-General's statistics for 1951, and it is among this small group of patients that cases of primary hyperoxaluria would presumably be found.

The high level of excretion of oxalate observed by us is clearly not a transient phenomenon, and the clinical histories of our patients suggest that it is present for many years and probably from birth.

The diagnosis of oxalosis during life is difficult, and we did not subject our patients to sternal puncture, although some other workers (e.g., Dunn 1955) have found calcium oxalate deposits in the sternal marrow post mortem. Examination of the eyes for crystalline oxalate deposits, an investigation suggested by the occurrence of cystine deposits in the anterior chamber in cystinosis, proved negative.

Primary hyperoxaluria appears to carry a bad prognosis: the urolithiasis and nephrocalcinosis are progressive, and recurrent episodes of pyelonephritis accelerate destruction of the renal parenchyma, leading to death from renal failure and hypertension in childhood or early adult life. Measurement of the urinary excretion of oxalate is necessary to distinguish these patients from cases of isolated urolithiasis occurring during early life which do not carry this grave prognosis. Early knowledge of the diagnosis is also of value in planning the long-term combined medical and surgical management of these cases.

Primary hyperoxaluria might be thought to result from a renal oxalate leak or from excessive metabolic formation of oxalate, some of the excess appearing in the urine. Oxalosis presumably results from a high concentration of oxalate ion in the body-fluids, which could theoretically result either from renal failure, with inability to excrete this anion, or from its excessive formation.

If oxalosis is primarily due to renal failure, it is surprising that it has never, to our knowledge, been reported as a manifestation of chronic kidney disease except where there is at least strong presumptive evidence that the latter has resulted from primary hyperoxaluria. We recently examined (through the courtesy of Dr. A. G. Stansfield) histological preparations of most of the tissues from a fatal case of polycystic kidney disease which had displayed all the usual clinical and pathological stigmata of renal failure, and we found no evidence of metastatic calcium oxalate deposits. It therefore seems to us more likely that the sequence of events in primary hyperoxaluria and oxalosis is that summarised under the heading

TABLE III—POSSIBLE SEQUENCE OF EVENTS IN PRIMARY HYPEROXALURIA TERMINATING IN RENAL FAILURE WITH OXALOSIS

Metabolic theory	*Renal theory*
Excessive formation of oxalate	Renal leak of oxalate
↓	↓
High concentration of oxalate ion in the body-fluids	Increased urinary excretion of oxalate
↓	↓
Increased urinary excretion of oxalate → Oxalosis	Urinary lithiasis, nephrocalcinosis, and recurrent pyelonephritis
↓	↓
Urinary lithiasis, nephrocalcinosis, and recurrent pyelonephritis	Renal failure and renal hypertension
↓	↓
Renal failure and renal hypertension	Retention of oxalate
	↓
	Oxalosis

"Metabolic theory" than that under the heading "Renal theory" in table III.

In view of the fairly uniform distribution of oxalate among the commoner foodstuffs (Andrews and Viser 1951) it appears unlikely that the persistently increased urinary excretion of oxalate in primary hyperoxaluria can be attributed to fluctuations in the dietary intake of the anion. Our later (unpublished) studies have revealed no evidence that primary hyperoxaluria results from the absorption of an abnormally large proportion of a given dose of oxalate from the gastro-intestinal tract.

Some experimental support for the view that the fundamental abnormality in primary hyperoxaluria is a metabolic error is given by our recent observation (to be published) that administration of sodium benzoate significantly diminishes the urinary excretion of oxalate by patients with primary hyperoxaluria. The rationale of this experiment is that glycine can, in appropriate circumstances, act as a precursor of glyoxylate and oxalate in vitro (Giovanni and Vantaggi Cozzari 1948, Nakada and Weinhouse 1953, Nakada et al. 1955, Weinhouse 1955), and that benzoate depletes the "pool" of available glycine in vivo by forming hippurate (see, for example, Arnstein and Neuberger 1951, Simkin and White 1957). Thus it appears possible that there may be an abnormal conversion of glycine to oxalate in primary hyperoxaluria.

Summary

Two cases of extensive urinary lithiasis starting in early childhood and associated with a persistently high urinary excretion of oxalate are described.

The term "primary hyperoxaluria" is suggested for such cases.

The natural history and possible ætiology of primary hyperoxaluria and its relationship to oxalosis are briefly discussed.

We are grateful to Mr. A. W. Badenoch for his help in the surgical management of both these cases: it is a pleasure to thank Prof. A. Wormall, F.R.S., for his helpful discussions of biochemical problems; and Miss L. E. Fraser, B.SC., and Mr. L. Rawlings for their skilled assistance.

References at foot of next column.

ADRENALINE-SECRETING NEUROBLASTOMA IN AN INFANT

GEORGE A. MASON
V.R.D., M.B. Durh., F.R.C.S.
LECTURER IN THORACIC SURGERY

J. HART-MERCER
M.B. Edin.
SENIOR LECTURER IN PATHOLOGY

E. JOAN MILLAR
M.B. Durh., F.F.A. R.C.S., D.A.
SENIOR ANÆSTHETIST, THORACIC SURGERY UNIT

LEONARD B. STRANG
M.B. Durh., M.R.C.P.
FIRST ASSISTANT, DEPARTMENT OF CHILD HEALTH

N. A. WYNNE
M.B. Durh., M.P.S.
LECTURER IN PHYSIOLOGY

KING'S COLLEGE, NEWCASTLE, UNIVERSITY OF DURHAM

WE wish to record an unusual clinical experience which may have an importance beyond its immediate interest. We have recently seen an infant with attacks of paroxysmal hypertension due to the release of adrenaline and noradrenaline from a large intrathoracic tumour. The tumour was successfully removed and proved to be not a phæochromocytoma but a histologically malignant neuroblastoma containing adrenaline and noradrenaline.

Case-record

CLINICAL HISTORY

The baby was the first child of healthy parents and was born at full term, weighing 7 lb. 4 oz. She thrived until the age of 5 months, when quite suddenly one day she became deathly pale, sweated profusely, and began to breathe rapidly. Within 6 hours the attack passed off, and she became normal again. 2 weeks later she had a similar attack, which also ended abruptly after 5 or 6 hours. She continued to have similar attacks with increasing frequency. In each attack pallor, rapid breathing, sweating, and obvious distress were evident. Each ended abruptly after about 6 hours, when she appeared happy and well again. Between the ages of 5 and 6 months she had six attacks and in the last she was admitted to hospital.

She was well nourished but acutely ill, with temperature 105°F and respirations 80 a minute. She was extremely irritable and sweating profusely. There was an area of slight dullness at the left lung base posteriorly. She had no cough and no added sounds in the chest, but a provisional diagnosis of pneumonia was made and a course of penicillin was started. 12 hours later she appeared perfectly normal, smiling, and pink (temperature 98·2°F). Radiography showed a large rounded posterior mediastinal tumour (fig. 1). Examination of the blood showed Hb 16 g. per 100 ml. and white cells 13,450 per c.mm. (lymphocytes 65%, polymorphs 35%, no abnormal cells).

DR. ARCHER AND OTHERS: REFERENCES

Andrews, J. C., Viser, E. T. (1951) *Food Res.* **16**, 306.
Aponte, G. E., Fetter, T. R. (1954) *Amer. J. clin. Path.* **24**, 1363.
Archer, H. E., Dormer, A. E., Scowen, E. F., Watts, R. W. E. (1957) *Clin. Sci.* (in the press).
Arnstein, H. R. V., Neuberger, A. (1951) *Biochem. J.* **50**, 154.
Barrett, J. F. (1942) *Lancet*, ii, 574.
Dunn, H. G. (1955) *Amer. J. Dis. Child.* **90**, 58.
Giovanni, T., Vantaggi Cozzari, L. (1948) *Bull. Soc. ital. Biol. sper.* **24**, 1100.
Hawk, P. B., Oser, B. L., Summerson, W. H. (1949) Practical Physiological Chemistry. 12th ed., Philadelphia; p. 738.
Lund, T. (1957) Personal communication.
— Reske-Nielsen, E. (1956) *Acta path. microbiol. scand.* **38**, 353.
Nakada, H. I., Friedmann, B., Weinhouse, S. (1955) *J. biol. Chem.* **216**, 583.
— Weinhouse, S. (1953) *Arch. Biochem.* **42**, 257.
Newns, G. H., Black, J. A. (1953) *Gt. Ormond St. J.* **5**, 40.
Registrar-General (1951) Statistical Review for England and Wales.
Simkin, J. L., White, K. (1957) *Biochem. J.* **65**, 574.
Weinhouse, S. (1955) *In* McElroy, W. D., Glass, H. B. A Symposium on Amino Acid Metabolism. Baltimore.

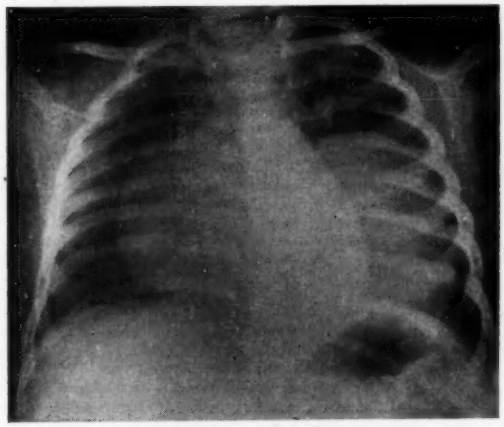


Fig. 1—Tumour projecting to left side.

First Attack in Hospital

On her 3rd day in hospital she became desperately ill again. She was pale, with grey cyanosis of her lips. Her skin felt cold and damp though her temperature was 101·4°F. The sweat soaked her clothes. Her respirations were 106 a minute and heart-rate 190. Her liver was enlarged to $2^1/_2$ in. below her costal margin and was tense and tender. Her blood-pressure was 120/80 mm. Hg. Electrocardiography showed rapid sinus rhythm, and she was regarded as having paroxysmal tachycardia with early congestive heart-failure. She was given oxygen and digitalis (digoxin 0·125 mg. 6-hourly). 8 hours later her rapid breathing and tachycardia receded, she became pink again, and her blood-pressure fell to 100/60.

At this stage a diagnosis of intrathoracic phæochromocytoma was suggested, the relatively small rise of blood-pressure being explained by the presence of heart-failure.

During the next 3 days she remained well, with a blood-pressure between 90/60 and 100/60 in both arms. Digitalisation was maintained. Bio-assay of a sample of urine at this time showed it to contain 0·08 μg. of free pressor amines per ml.—equivalent to an output of 56 μg. in 24 hours (average 24-hour output of urine 700 ml.). In this and all subsequent urinary bio-assays the pressor amines were assayed as noradrenaline.

Second Attack in Hospital

On the 6th day in hospital she became ill again, with the same appearance as before. Her heart-rate was now 170 and blood-pressure between 135/90 and 140/90 mm. Hg. It was decided to try the effect of phentolamine (' Rogitine '). While one observer recorded the systolic blood-pressure, a second injected phentolamine 1 mg. directly into a scalp vein. This produced (fig. 2) a temporary fall of the systolic blood-pressure to 110 mm. Hg at 30 seconds, with a gradual return to 140 mm. Hg at $2^1/_2$ minutes. The test was repeated with phentolamine 1·5 mg., the systolic blood-pressure being lowered to 100 mm. Hg. This brought the clinical evidence of the attack to an abrupt end.

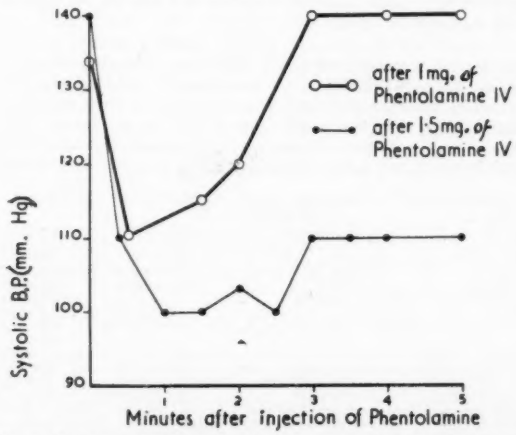


Fig. 2—Response of systolic blood-pressure to phentolamine during episode of hypertension.

Bio-assay of a catheter specimen of urine taken immediately showed it to contain 1 μg. of pressor amines per ml.—equivalent to 700 μg. in 24 hours.

Although this confirmed the diagnosis of an adrenaline-secreting tumour, it was obvious that this copious excretion of pressor amines was only paroxysmal, and it was thought desirable to collect urine over a full 24 hours for bio-assay. This was done with an indwelling catheter. During this collection no attacks occurred and the amount of urine passed was 700 ml. Bio-assay of this sample showed it to contain 120 μg. of free pressor amines. Normally at this age about 13·2 μg. of free pressor amines is excreted in the urine in 24 hours (Farquhar et al. 1956).

A diagnosis of intrathoracic phæochromocytoma was made, although it was considered curious that persistent hypertension was not present with a tumour so large and constantly moved by the heart and diaphragm.

Operation

After consultation a thoracotomy was performed. A large pink smooth rounded tumour was found in the posterior mediastinum. It arose from the left sympathetic chain and appeared to have filamentous connections entering several intervertebral foramina. Removal was macroscopically complete.

Careful plans had been made to deal with sudden fluctuations of blood-pressure during operation. Intravenous blood was given in one leg, and in the other an infusion was set up which could be connected by a two-way tap to one of two chambers, one containing 0·8 mg. of noradrenaline per 100 ml. of 5% glucose, the other containing 5% glucose only. A second two-way tap was included between this arrangement and the baby, through which phentolamine could be injected as required from a syringe. The systolic blood-pressure was recorded every 1–2 minutes.

In the early stages of the operation, as the tumour was being handled, the blood-pressure rose to 150–160 mm. Hg, and phentolamine 2·5 mg. was given in three divided doses. This lowered the systolic blood-pressure to 110 mm. Hg. As the tumour was removed, the systolic blood-pressure fell to 60 mm. Hg, and noradrenaline 0·3 mg. rapidly restored the blood-pressure to a satisfactory level.

Subsequent Course

After operation the blood-pressure rose to 180/100 mm. Hg. This rise was uninfluenced by as much as 5 mg. of phentolamine intravenously. There was, however, no particular distress associated with the hypertension and no excessive sweating. During the next 24 hours the blood-pressure fell to 130/85 mm. Hg and during the next 3 days to 115/80 mm. Hg. 7 days after operation the pressure had fallen to a consistent level of 90/60.

After another week the urine was again collected over 24 hours with an indwelling catheter. Bio-assay showed it to contain 20 μg. of pressor amines in the 500 ml. of urine collected over this period.

During the 12 months since operation the baby has thrived. She has had no further attacks of pallor, sweating, or dyspnœa, and her blood-pressure has remained consistently at 90/60 mm. Hg. The temporary postoperative hypertension was not explained, but we have observed a similar postoperative rise of blood-pressure following other intrathoracic operations. There has been no sign of recurrence or metastasis.

Assay of Tumour

The tumour weighed 50 g., and bio-assay showed it to contain 0·14 mg. of pressor amines per gramme of tumour. 48% of these pressor amines was noradrenaline. No 3-hydroxytyramine was detected using paper chromatography methods on extracts of the tumour. The solvents used were phenol/water and *n*-butanol/acetic acid/water. The spraying reagents used included potassium ferricyanide and potassium iodate.

PATHOLOGY

The operation specimen consisted of the main mass of the tumour, a largely encapsulated solid fleshy growth of homogeneous pinkish-grey colour, together with smaller fragments of similar tissue and a piece of bone 2·5 cm. long. Six blocks, including one of bone, were fixed in 10% formol-saline and one in 3% potassium-dichromate solution with formalin (regrettably not without slight risk of partial fixation by

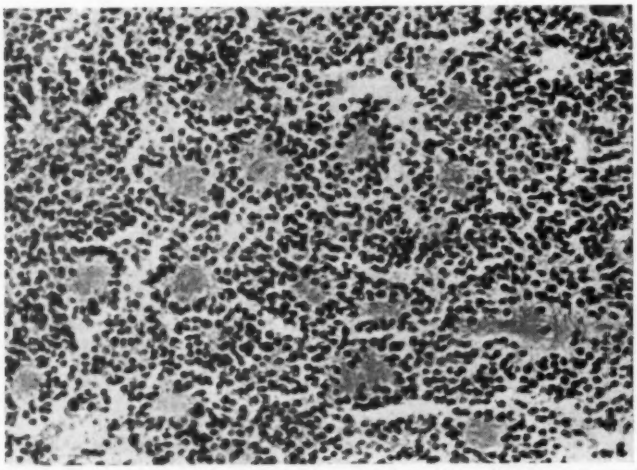


Fig. 3—Section of neuroblastoma showing pseudo-rosettes. (Hæmatoxylin and eosin. ×180.)

previous contact with formalin). Short serial groups of paraffin sections were prepared from tumour blocks at intervals ranging from 60 μ to 240 μ. Most of the sections were stained with hæmalum and eosin, but some, particularly those fixed with dichromate, were stained with Giemsa. Other stains and methods included hæmalum and van Gieson, Mallory's connective tissue stain, von Kossa, the Prussian-blue reaction, Schmorl's ferricyanide method, and Fontana's ammoniacal silver solution.

Classification of Tumour

There was no immediate difficulty in classifying the tumour. All six blocks from the growth showed a microscopically characteristic (because generally well-differentiated) neuroblastoma or, more exactly perhaps, sympathicoblastoma. The diagnosis caused surprise since a phæochromocytoma had been expected; and in view of the unusual clinical and chemical associations of the growth a more detailed descriptive record may be required than would otherwise be deemed necessary.

Histological Appearances

Partly enclosed by a fibrous capsule and supported perhaps more by its network of small blood-vessels than its scant fibrous trabeculæ, the tumour parenchyma presented the familiar highly cellular appearance of neuroblastoma. A few cells were small, with darkly staining spherical nuclei and little cytoplasm, primitive-looking cells often compared with normal sympathogonia. The great majority, however, comparable more or less to sympathoblasts, were of somewhat larger size, with larger pale nuclei and sometimes more obvious cytoplasm. Here and there, on high magnification, tapering cytoplasmic projections could be traced a short distance into the tangled neurofibrillary tissue surrounding the blood-vessels and forming the core of the numerous and mostly well-differentiated pseudo-rosettes (fig. 3). Mitoses were very rarely encountered, but giant, convoluted, or multiple nuclei were frequently seen. Grossly necrotic areas, often noted in neuroblastoma, were not found, but close scrutiny showed widely scattered collections of nuclear detritus. Small foci of calcification were numerous, sometimes attended by histiocytes or by multinucleated giant cells.

Perivascular infiltrations of lymphocytes were commonly seen as well as an occasional eosinophil leucocyte and very rarely a neutrophil. Histiocytes thinly but widely scattered through the growth occasioned some difficulty, for some at least rather resembled the early forms of phæochromocyte seen, for example, in the fœtal organ of Zuckerkandl. The cells contained abundant granular cytoplasm of rounded or polygonal outline and a nucleus distinguishable from those of the tumour sympathoblasts by its still more vesicular appearance and its content of one nucleolus or occasionally two distinct nucleoli. Later study, however, revealed their frequently close association with blood-vessels, ingestion of nuclear material, and the development of foamy cytoplasm. They were, moreover, thinly scattered, nowhere forming whorls or nests, and their cytoplasm never revealed chromaffin granules in the dichromate-fixed block.

Chromaffin Reaction

Besides arterioles, capillaries, and venules of familiar aspect, convoluted thick-walled vessels of the kind frequently noted in glioblastoma were observed. Large cavernous venous spaces lined only by a thin layer of endothelium were also found, and into these projected naked masses of well-organised tumour tissue. In addition to obvious areas of hæmorrhage sometimes accompanied by traces of hæmosiderin there were collections of blood lying in clefts between lines of naked tumour cells forming the periphery of organised tumour formations. Whether these were also hæmorrhages or part of the circulation of the growth remains perhaps conjectural; but it was just in these naked lines of tumour sympathoblasts that a faint, but on high magnification distinct, chromaffin reaction was obtained.

The reaction was first detected on close scrutiny of Giemsa-stained sections; some of the tumour sympathoblasts contained numerous very minute greenish-brown or greenish-yellow granules. Later it could be detected in the hæmalum and eosin preparations as a faint yellow-brown granular pigmentation partially obscured by the eosin. The pigment behaved like an adrenochrome in reducing potassium ferricyanide (Schmorl's reaction) but has so far failed to reduce ammoniacal silver solutions. No tumour ganglion cells had apparently developed; in one block mature ganglion cells were seen accompanied by nerve-fibres offering such sharp contrast with the surrounding tumour cells that no doubt was felt that they were the residue of a local sympathetic ganglion.

Metastasis

The accompanying specimen of bone appeared free from tumour infiltration. On the other hand, intravascular growth within the primary tumour has already been mentioned and in one area a local small lymph-node contained growth.

Discussion

Phæochromocytoma, although rare in childhood, appeared to be a reasonable preoperative diagnosis in the present case. Forty-seven published cases under the age of 16 years have been collected by Tvetoglu and Lee (1956), and Robinson and Williams (1956) in adding two more cases have reviewed the subject. A neuroblastoma secreting adrenaline and noradrenaline has not previously been reported. Nevertheless the paroxysmal hypertension associated with increased urinary excretion of pressor amines, and the extraction of pressor amines from the tumour itself, with the characteristic histological picture and the postoperative decrease in excretion of urinary pressor amines and fall of blood pressure to normal levels with no further paroxysms leave no doubt that in this child a neuroblastoma did secrete adrenaline and noradrenaline.

The site of production of the pressor amines in this tumour is a matter of some interest. No phæochromocytes were identified such as Wahl (1914) apparently found in one case of neuroblastoma, and we must conclude that either they were overlooked, or, as we think more likely, the pressor amines were produced by relatively undifferentiated cells—certainly if the positive chromaffin

COMPARISON OF PRESSOR AMINE CONTENTS OF DIFFERENT TISSUES

Tissue or organ	Content of pressor amines (mg. per g. of tissue)	Total amount of pressor amines in tumour or organ (mg.)
Neuroblastoma (present case)	0·14	7·0
Phæochromocytoma in 2 children	0·74–1·37	11·8–30·14
Phæochromocytoma in adults	0·67–15	..
Adrenal glands of baby aged 6 mos.	..	0·019
Organ of Zuckerkandl of baby aged 6 mos.	..	0·015
Adrenal gland of adult	0·11–0·67	..

reaction in some of these cells is to be believed. This positive reaction should, however, be accepted with some reserve, for the tissue block fixed in dichromate solution was taken from the centre of the tumour mass only after it had lain in formalin for some hours. Apparently unfixed it could not be guaranteed completely unaffected by the formalin, and it is now generally agreed (Lillie 1948, Pearse 1953) that prior formalin fixation interferes with the chromaffin reaction. Willis (1948) indeed warns that both false positive and false negative results may be obtained.

The cells in which we obtained the positive chromaffin reaction could equally well correspond to early sympathoblasts or phæochromoblasts, for initially these are apparently indistinguishable (Coupland 1952). But, as Coupland (1952) observes, chromaffin granules are not normally found before the phæochromocytes have attained a considerable degree of morphological maturity.

Yet too close a parallelism should not perhaps be expected between the cells of an embryonic neoplasm and those of the corresponding normally differentiating tissue. This is not the first example of a neuroblastoma with chromaffin-positive primitive cells; Blacklock (1934) found, among his group of differentiated neuroblastomas, occasional small nests of tumour neuroblasts which gave a rather indefinite chromaffin reaction.

The pressor-amine content of the neuroblastoma in the present case can be compared with that of several tissues and tumours which have been reported in the literature. These data, summarised in the accompanying table, are for phæochromocytoma in children (Robinson and Williams 1956), adrenal glands and the organ of Zuckerkandl in babies aged 6 months (West et al. 1953), and for adult adrenal glands (West and Taylor 1955). In the present case the content of pressor amines per gramme of tissue was lower than that in phæochromocytoma and in normal adrenal; but, owing to the large size of the tumour, the estimated total content was considerable.

The child we have described is alive and in normal health 12 months after removal of a histologically malignant tumour. The occasional spontaneous and post-operative regression of neuroblastoma, even when metastases are present, is recognised but unexplained (Farber 1940, Koop et al. 1955), and it has long been known that this tumour may rarely differentiate into ganglioneuroma (Cushing and Wolbach 1927).

We intend to examine further similar tumours for adrenaline, noradrenaline, 3-hydroxytyramine, and 3 : 4 dihydroxyphenylalanine to see if the clinical picture and malignancy of these tumours are related to the presence or absence of any of these substances.

Summary

A baby with an adrenaline-secreting intrathoracic tumour is described.

The tumour was successfully removed and proved to be a neuroblastoma, whose histology is described in detail.

The child survives with no sign of recurrence.

We wish to thank Prof. S. D. M. Court and Dr. F. J. W. Miller, under whose care the baby was first admitted, for their helpful criticism, and Dr. S. Whately Davidson for his radiological advice.

REFERENCES

Blacklock, J. W. S. (1934) *J. Path. Bact.* **39**, 27.
Coupland, R. E. (1952) *J. Anat.* **86**, 357.
Cushing, H., Wolbach, S. B. (1927) *Amer. J. Path.* **3**, 203.
Farber, S. (1940) *Amer. J. Dis. Child.* **60**, 749.
Farquhar, J. W., Crawford, T. B. B., Law, W. (1956) *Brit. med. J.* ii, 276.
Koop, C. E., Kiesewetter, W. B., Horn, R. C. (1955) *Surgery*, **38**, 272.
Lillie, R. D. (1948) Histopathologic Technic. Philadelphia and Toronto; p. 103.
Pearse, A. G. E. (1953) Histochemistry. London; p. 346.
Robinson, M. J., Williams, A. (1956) *Arch. Dis. Childh.* **31**, 69.
Tvetoglu, F., Lee, C. H. (1956) *Amer. J. Dis. Child.* **91**, 365.
Wahl, H. R. (1914) *J. med. Res.* **30**, 205.
West, G. B., Shepherd, D. M., Hunter, R. B., MacGregor, A. R. (1953) *Clin. Sci.* **12**, 317.
— Taylor, N. A. W. (1955) *Glasg. med. J.* **36**, 123.
Willis, R. A. (1948) Pathology of Tumours. London; p. 873.

MASSIVE SPONTANEOUS INTRAPERITONEAL HÆMORRHAGE IN LATE PREGNANCY

OWEN E. OWEN
M.B. Edin., F.R.C.S.

JOHN A. HOLMES
M.B. N.U.I., M.R.C.O.G.

T. J. SCANNELL
M.B. N.U.I., D. Obst.

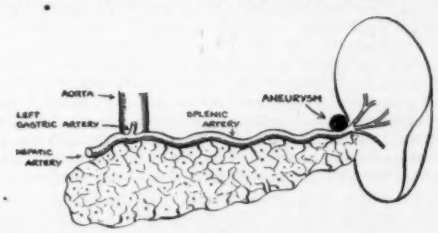
From St. James' Hospital, Balham, London

SPONTANEOUS massive hæmorrhage into the peritoneal cavity in late pregnancy is rare, but often fatal. Our aim is to recall the condition to the minds of obstetricians and to present 2 cases of unusual interest.

Ruptured Splenic Aneurysm

Case 1.—A woman, aged 23, was admitted to St. James' Hospital as an emergency, when twenty-six weeks advanced in her first and hitherto uneventful pregnancy. Two hours previously, sudden severe pain had begun in the epigastrium, radiating to the left shoulder. She soon felt weak and fainted, but regained consciousness before arrival in hospital, when she looked pale and shocked. She continuously changed her position on the examining couch, and severe epigastric pain made her cry out. Her pulse-rate was 100 a minute and the blood-pressure 108/60 mm. Hg. There was generalised abdominal tenderness, most severe in the epigastrium and left hypochondrium. The uterus felt of normal consistence. No fœtal heart-sounds were heard. The percussion-note was dull in the flanks. Bowel sounds were heard. There was no abnormality on pelvic examination. The urine contained a trace of albumin.

Since intraperitoneal hæmorrhage was suspected, blood-transfusion was begun, and laparotomy then carried out through a right paramedian incision. The peritoneal cavity was filled with blood. The uterus was enlarged to correspond with a twenty-six-week gestation and otherwise normal. When the peritoneal cavity had been mopped clear of blood, fresh blood welled up from the left upper quadrant. The incision was extended transversely to the left costal margin. The spleen felt normal, but a firm round swelling $1^1/_2$ cm. in diameter was felt on the splenic artery close to its division into its main branches. This was thought to be an aneurysm of the splenic artery which had ruptured (see figure). At this



The position of the aneurysm in case 1.

stage, the patient was collapsed and pulseless. A long curved Parker-Kerr clamp was applied across the splenic vessels proximal to the aneurysm, and further clamps immediately distal to it and across the splenic hilum; these controlled the bleeding. Blood was now being given intravenously by three leads. A normal spleen was removed. The tissue in the clamps was stitch-ligated and an additional ligature was applied proximal to the aneurysm. The abdomen was closed in layers, with drainage to the splenic area, in view of possible injury to the tail of the pancreas. The time between the patient's first symptoms and the operation was five hours. She recovered from her shock and made uneventful progress. Six weeks later, she miscarried a macerated fœtus. She has since given birth to a normal infant.

Discussion

Of all recorded cases of ruptured splenic aneurysm, 11% ruptured in pregnancy, and in 20% of those in

females, the patient was pregnant at the time of the rupture (Sherlock and Learmonth 1942).

Owens and Coffey (1953) reviewed the literature on ruptured splenic aneurysm in pregnancy and collected 32 cases. We have found 7 further cases in the literature including the present case. Zummo et al. (1952) reported 2 cases, and Tomsykoski et al. (1953), Gallagher and Hudson (1954), and Tanner and Miller (1955), have each reported a case. Of the 39 patients, only 5 survived. Moreover, many fatal cases are probably never reported. The condition carries a very high mortality, but the poor prognosis may be improved by greater awareness of the condition and by early and adequate treatment.

Diagnosis

The ætiology of splenic aneurysms and their liability to rupture during pregnancy have been discussed previously (Owens and Coffey 1953, Sherlock and Learmonth 1942); and here we are particularly concerned with diagnosis and treatment.

An aneurysm may cause epigastric pain and occasional vomiting. There may be a systolic murmur in the left hypochondrium and a radiograph may show concentric calcification in the splenic region. As the symptoms are often obscured by the pregnancy, however, diagnosis is unlikely unless the aneurysm ruptures.

Rupture usually follows some slight exertion. The rupture may take place in two stages—in 12·5% of cases according to Sherlock and Learmonth (1942): the initial hæmorrhage ceases spontaneously, clotting takes place around the aneurysm, and a false aneurysm is formed; this initial episode may then be followed many days later by a more severe attack of bleeding (Gillam 1942).

More commonly, the aneurysm ruptures without warning. A constant feature is sudden severe pain in the epigastrium or left hypochondrium. Vomiting may follow. The aneurysm sometimes ruptures into a viscus but usually into the lesser sac, from whence the blood reaches the greater sac. The abdominal pain then becomes more generalised, though it is always worst in the epigastrium or left hypochondrium. There is clinical evidence of progressive bleeding—pallor, air hunger, increasing pulse-rate, and falling blood-pressure. The patient may die from exsanguination in ten to fifteen minutes (Nodes and Hinds 1900), but there is usually an interval of some hours before death. The uterus may be of normal consistence, but it is sometimes tense and tender (Lennie and Sheehan 1942), and in such cases, concealed accidental hæmorrhage may be diagnosed.

At first, the condition may be confused with coronary thrombosis, gall-stone colic, perforated peptic ulcer, or a similar catastrophe. In 14 of the reported cases, no diagnosis was made; the others were diagnosed as concealed accidental hæmorrhage (7), ruptured uterus (5), intraperitoneal hæmorrhage (3), rupture of major artery or spleen (2 each), ruptured splenic aneurysm (1), ruptured ectopic gestation (1), bleeding from splenic region (1), gall-stone colic (1), ruptured viscus (1), and reaction to sedatives (1). In most cases where no diagnosis was made, the patient was dead or moribund when first seen.

Valuable time was often wasted because of an incorrect diagnosis. In the 7 cases diagnosed as concealed accidental hæmorrhage conservative treatment was followed by death. The two conditions may resemble each other closely, and in any case where there is doubt, the membranes should be punctured without delay.

Ruptured uterus was the diagnosis in 5 cases and intraperitoneal hæmorrhage from different sources in 10 cases. Of the 5 patients who survived, 3 were operated on within five hours of the onset; in the other 2, the interval between onset and operation was not stated.

Treatment

Blood-transfusion and oxygen are important initially, but they are useless unless the correct surgical treatment follows.

Of the 39 patients, 19 were subjected to operation: splenectomy (6), cæsarean section (4), cæsarean section with splenectomy (2), supravaginal hysterectomy (2), laparotomy and tamponade (2), cæsarean section and tamponade (1), vaginal hysterectomy (1), and laparotomy only (1). It is worth remarking that the 5 patients who survived were among the 6 treated by ligation of the splenic artery and splenectomy (see table). Although Chalmers (1949) and Lennie and Sheehan (1942) advise preliminary cæsarean section in the later weeks of pregnancy, this seems unnecessary and might waste valuable time. We feel that, had preliminary cæsarean section been done in our patient, she would not have survived.

SUCCESSFULLY TREATED CASES OF RUPTURED SPLENIC ANEURYSM IN PREGNANCY

Authors	Gestation (weeks)	Symptoms	Onset-operation interval (hr.)	Treatment
McLeod and Maurice (1940)	28	Severe pain in left hypochondrium, collapse	5	Splenectomy
Gillam (1942)	Puerperium	Collapse, severe epigastric pain	4	Splenectomy
Hogeman (1943)	..	..	..	Splenectomy
Gallagher and Hudson (1954)	20	Intense upper abdominal pain, collapse	..	Splenectomy
Owen et al. (1957)	26	Severe epigastric pain, collapse	5	Splenectomy

Satisfactory exposure of the splenic region is obtained by a long paramedian incision with a transverse extension. The uterus may be eventrated if its bulk hampers the surgeon (McLeod and Maurice 1940). To palpate the splenic artery, the gastrocolic omentum is divided and the lesser sac exposed. Palpation of the course of the splenic artery along the upper border of the pancreas is probably the most helpful manœuvre in locating the aneurysm. Particular attention should be given to the region of its main divisions. The bleeding is controlled by applying proximal and distal clamps, applied by feel rather than under direct vision.

The importance of the distally placed clamp is not always appreciated. Lennie and Sheehan (1942) and Poidevin (1955) recommend ligation of the splenic artery proximal to the rupture, the spleen being left in situ; but the collateral circulation, reaching the spleen by the vasa brevia and the left gastro-epiploic artery, is enough to cause brisk bleeding within minutes if only a proximal ligature is applied. This has been demonstrated many times by one of us (O. E. O.) when operating on bleeding gastric ulcers that erode the splenic artery. In some cases where no definite aneurysm is felt, it will be advisable to ligate the splenic artery as close to its origin as possible at an early stage, and to place sutures distal to the bleeding point when the major hæmorrhage is controlled.

Rupture of Vein in Recurrent Secondary Abdominal Pregnancy

Case 2.—A woman, then aged 28, had a secondary abdominal pregnancy in another hospital at twelve weeks' gestation in 1948. In 1956, she was admitted to St. James' Hospital as an emergency at twenty-eight weeks' gestation, after a normal antenatal period. She complained of severe pain in the centre of the abdomen. She was pale and shocked and the blood-pressure was 70/40 mm. Hg. There was abdominal tenderness and guarding, and a dull percussion note all over the abdomen. The uterus could not be well outlined. No bowel sounds and no fœtal heart were heard. There was no vaginal bleeding. Intraperitoneal hæmorrhage was suspected, a blood-transfusion was started, and the abdomen was opened through a right paramedian incision.

The peritoneal cavity was filled with blood. A twenty-eight-week abdominal pregnancy was lying behind a slightly enlarged uterus. Large tortuous veins coursed over the gestation sac, one of which was bleeding briskly. The placenta was membranous, and attached to the left fallopian tube, the left broad ligament, and the mesosigmoid. The sac was opened and a dead fœtus weighing 3 lb. 1 oz. was extracted. Bleeding was controlled by gathering the collapsed gestation sac into the hand and gripping it firmly. The base of the sac was transfixed and ligated and the excess tissue excised. The attachment of the membranous placenta to the sigmoid mesocolon, rectum, and broad ligament was not disturbed. The wound was closed with a wide corrugated drain into the pelvis.

Altogether, 60 oz. of blood was removed from the peritoneal cavity. 2½ litres of blood was transfused. The mother made

an uneventful recovery and was discharged after twelve days. Salpingograms, done twice after discharge, showed no patency in the tubes.

Discussion

We have been unable to find an earlier recorded instance of two secondary abdominal pregnancies in the same patient. In advanced abdominal pregnancy, rupture of the gestation sac is always a danger. If the rupture does not involve a vessel, an episode of abdominal discomfort is all that transpires. If a vessel is torn, severe intraperitoneal hæmorrhage may follow, as in this case and in others (Haynes and Nabors 1956).

In case 2 the abdominal pain was more central and less intense than in case 1, but the shock and the signs of intraperitoneal hæmorrhage were similar. Again, early laparotomy and control of the bleeding-point proved effective. In case 2, the bleeding-point was accessible and was secured without difficulty, in contrast to the troubles encountered in case 1.

Summary

2 examples of spontaneous intraperitoneal hæmorrhage during late pregnancy were clinically similar but different in the source of the bleeding. In such circumstances concealed accidental hæmorrhage is often diagnosed and the correct treatment is delayed, with disastrous results. Early puncture of the membranes may help to avoid this danger.

The diagnosis and treatment are reviewed of ruptured splenic aneurysm in pregnancy. 4 successfully treated cases are summarised and an additional case is presented.

We wish to thank Miss I. R. Bishop for allowing us to treat these cases and for permission to publish the case-reports. We also thank Mrs. Mace for the diagram.

REFERENCES

Chalmers, J. A. (1949) *Brit. J. Surg.* **37**, 86.
Gallagher, H. W., Hudson, K. (1954) *Brit. med. J.* ii, 1209.
Gillam, J. F. E. (1942) *Ibid*, i, 69.
Haynes, D. M., Nabors, G. C. (1956) *Sth. med. J., Nashville*, **49**, 619.
Hogeman, K. E. (1943) *Nord. Med.* **17**, 189.
Lennie, R. A., Sheehan, H. L. (1942) *J. Obstet. Gynæc., Brit. Emp.* **49**, 426.
McLeod, D., Maurice, T. (1940) *Lancet*, i, 924.
Nodes and Hinds (1900) *Trans. obstet. Soc. Lond.* **42**, 305.
Owens, J. C., Coffey, R. J. (1953) *Surg. Gynec. Obstet.* **97**, 313.
Poidevin, L. O. S. (1955) *Med. J. Aust.* **1**, 922.
Sherlock, S. P. V., Learmonth, J. R. (1942) *Brit. J. Surg.* **30**, 151.
Tanner, F. N., Miller, H. B. (1955) *Neb. St. med. J.* **40**, 9.
Tomsykoski, A. J., Stevens, R. C., Izzo, P. A., Rodriquez, C. E. (1953) *Amer. J. Obstet. Gynec.* **66**, 1264.
Zummo, B. P., Williams, P. C., Uznauski, M. (1952) *Surg. Gynec. Obstet.* **95**, 512.

Reviews of Books

Chronic Bronchitis in Newcastle upon Tyne

A. G. OGILVIE, M.D., F.R.C.P.; D. J. NEWELL, M.A. Edinburgh: E. & S. Livingstone. 1957. Pp. 115. 15*s*.

THOUGH chronic bronchitis is responsible for many deaths and great loss of working-time, only in the last decade has it attracted more than scant attention from research-workers. Attempts to unravel the ætiology of this common disease are welcome. A valuable contribution has been made by Dr. Ogilvie and Mr. Newell, of the Royal Victoria Infirmary, Newcastle upon Tyne, who have carried out a survey to discover the prevalence of the disease, its clinical pattern, and the factors important in its ætiology.

A sample of the population consisting of every 40th house was used. The initial ascertainment and social inquiry was made by the health visitors. Chronic bronchitis was recognised when there was cough with sputum persistent throughout the winter or throughout the year, in the absence of other causal respiratory disease, the symptoms having been present for at least two years. Patients under the age of 30 were excluded. For every presumptive bronchitic patient a comparable random control was chosen. Both the bronchitics and the controls were medically examined, and the diagnosis of chronic bronchitis and the absence of chronic bronchitis among the controls was confirmed.

The prevalence of bronchitis was 36% for men aged 30 or over and 17% for women of the same age-group. A comparison between 464 bronchitic patients and 485 non-bronchitic patients showed that the following factors were more common in the bronchitic than the non-bronchitic group: a personal history of allergy, a family history of bronchitis, asthma, cigarette-smoking, sooty, damp, and foggy living conditions, and extremes of temperature, draughts, and dusty atmosphere at work. A significant preponderance of bronchitic patients were found in social class v, but there was no relationship between the standard of personal domestic care, housing, and particular occupations on the one hand and bronchitis on the other.

Dr. Ogilvie and Mr. Newell believe that there are two stages in chronic bronchitis: the first is potentially reversible; the second is irreversible and is characterised by a progressive obliterative bronchiolitis. They found that though a constitutional predisposition to the disease exists, which may be hereditary, infection is the dominating factor in chronic bronchitis and is maintained by environmental factors, such as cigarette-smoking, atmospheric pollution, dust, draughts, and extremes of temperature at work. If these causes were removed the disease might often be arrested before irreversible change occurred.

A better understanding of the ætiological factors of chronic bronchitis will be attained only by careful trials such as this, and the authors are to be congratulated on the careful planning and attention to detail that was given to this survey.

Drug Resistance of Microorganisms

ROBERT J. SCHNITZER, EMANUEL GRUNBERG, depart- of chemotherapy, Hoffmann-La Roche Inc., Nutley, New Jersey. New York: Academic Press. London: Academic Books. 1957. Pp. 395. 80*s*.

THE discoverer of chemotherapy, Ehrlich, found not only that pathogenic organisms could be destroyed in the body by suitable chemical compounds, but also that the organisms often adapted themselves to this attack and became resistant to the drugs which had formerly killed them. The phenomenon of drug-resistance was thus first studied in trypanosomes. Later, when effective chemotherapeutic remedies against bacteria were discovered, the same problems were met; and bacteria resistant to sulphonmiades or to penicillin exercised the wits of research-workers in the laboratory and of clinicians in the ward. Dr. Schnitzer and Dr. Grunberg have now skilfully collected all the extensive information on this subject in readable form.

General conclusions are usually difficult to draw, because the combinations of drug, organism, and technique are infinite in number and because the behaviour of the organisms themselves varies on different occasions. Moreover the worker is dealing not with individual organisms, but with the large and changing populations which make up a strain of bacteria or protozoa. Fundamentally two processes seem to be at work—mutation or inheritable change in the individual organisms, and selection of such changed individuals and their progeny by the continued action of the drug. Controversy has raged over the relative importance of these two processes, but Dr. Schnitzer and Dr. Grunberg conclude that with bacteria at any rate both are probably involved, though mutation is probably the more important process of the two. The changes which take place when organisms become drug-resistant are of many kinds according to the organism and the drug. In some cases—e.g., with trypanosomes and arsenicals—the organism absorbs less of the drug. In other cases—e.g., bacteria and sulphonamides—the organisms may develop different metabolic pathways. In yet other cases—e.g., with some penicillin-resistant bacteria—an enzyme destroying the drug may be produced.

The book has a good index and an extensive bibliography. Its format is pleasing. It is a valuable review of a wide and often perplexing field of research.

A Mental Health Handbook

IAN SKOTTOWE, M.D., M.R.C.P., D.P.M., psychiatrist, Warneford and Park Hospitals, Oxford. London: Edward Arnold. 1957. Pp. 196. 21*s*.

THERE is evidently a recurring need for simple accounts of what psychological medicine is and what it can do. Dr. Skottowe's book meets this need admirably, for it is sensible, well informed, and straightforward. No-one looks for brilliance and originality, or for profundity and critical scholarship, in a semi-popular handbook of this type: such qualities would impair its usefulness to the medical and lay people in contact with work on mental health to whom it is addressed.

After a general account of how mental health and mental illness are viewed by the psychiatrist and what social factors and social actions are effective in promoting mental health, Dr. Skottowe suggests ways in which the needs of various localities might be met. With practical wisdom, he advocates making better use of what we have rather than embarking on costly new ventures. Health visitors, social workers, and others engaged in public-health activities will appreciate his realistic approach to the tasks that confront them in developing the psychiatric side of their duties. The only sign of unorthodoxy lies in the book's support for widespread anthropometry, on the lines developed by the research group to which Dr. Skottowe belongs: he believes its use would serve to indicate some types of vulnerability and to show the spheres of action in which an individual would be best able to fulfil his potentialities.

Acoustic Nerve Tumours

J. LAWRENCE POOL, M.D., professor of neurological surgery, Columbia University; ARTHUR A. PAVA, M.D., assistant neurological surgeon, Wesson Memorial Hospital, Springfield, Massachusetts. Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1957. Pp. 161. 42*s*.

THIS easily read monograph sets out the experience of the authors, and others, in the field of the acoustic neurinoma.

A brief historical account is followed by a detailed description of the pathology, and the symptoms and signs, which are reviewed chronologically, and by an assessment of the value of various diagnostic procedures. Six atypical case-records are included.

The authors describe their operative technique and post-operative management and discuss morbidity and mortality. They seem to favour total removal of the tumour, apart from certain clear contra-indications, though in practice only 39 out of 162 operations were total extirpations. They also give an account of their technique of facial-nerve anastomosis to the 11th or preferably the 12th nerve. These procedures, they say, "have been almost always successful with marked restoration of facial tone and symmetry in all cases." Unfortunately this has not been the experience of many other surgeons.

The monograph ends with a rather crowded discussion of the differential diagnosis and a short note on bilateral eighth nerve tumours.

The diagrams and photographs are remarkably clear, and the tables have been compiled with equal care.

The trouble that has been taken to gather into this book all the useful knowledge on this subject is reflected in the extensive bibliography.

Recent Outbreaks of Infectious Diseases

S. LEFF, M.D., D.P.H., barrister at law, medical officer of health, borough of Willesden. London: H. K. Lewis. 1957. Pp. 408. 35*s*.

IN this book Dr. Leff has collected epidemiological data on recent outbreaks of smallpox, poliomyelitis, Q fever, psittacosis, Bornholm disease, typhoid and paratyphoid fevers, food-poisoning of salmonella and staphylococcal origin, and diphtheria; and he has added chapters on lead-poisoning caused by the use of waste battery-casings as domestic fuel, and on smog, particularly the London fog of 1952. A short general description of each disease is followed by a highly detailed account of the epidemiological investigations made in these outbreaks, and the lessons learned from the negative and positive findings. This should be useful to medical officers of health and other epidemiological workers; the detail is more for the specialised than for the general reader. Dr. Leff stresses the rising incidence of food-poisoning; it is surprising to learn that there were more food-poisoning outbreaks in 1955 in school canteens than in all hospitals, restaurants, and cafés together.

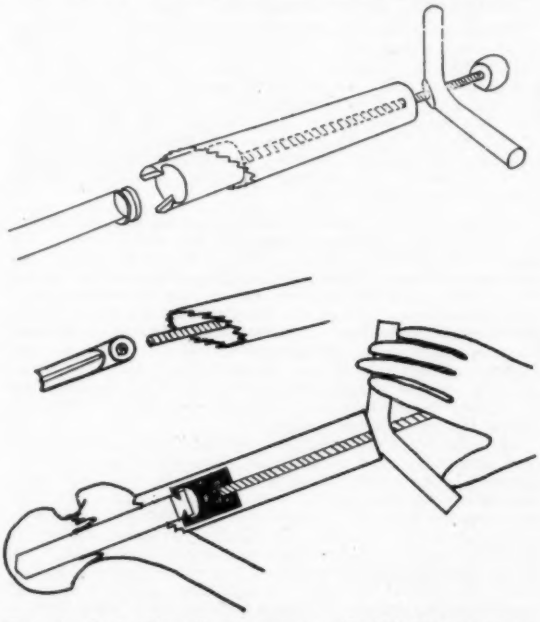
The book is well produced, the epidemiological references are many, and there is a good index.

Sports Injuries (Bristol: John Wright & Sons. 1957. Pp. 204. 35*s*.).—Injury, says Mr. D. F. Featherstone, is the occupational hazard of sport. In this book he has drawn on his experiences as physiotherapist to several football and cricket teams to suggest methods whereby the incidence, severity, and disabling sequelæ of common sports injuries can all be reduced. He is particularly concerned with the professional player who is treated intensively by a full-time physiotherapist. But, because he considers as well the amateur who receives such expert attention only occasionally, the book will be of interest to all concerned with the medical care of athletes.

New Inventions

PIN EXTRACTOR

Smith-Petersen pins occasionally have to be extracted, either during the operation or subsequently. An instrument for extracting Smith-Petersen, MacLoughlin, and similar pins is shown in the accompanying figures.



The chuck is slipped sideways so that its lips engage the groove around the head of a Smith-Petersen pin. The barrel fits closely, preventing the pin from slipping out. The chuck can be unscrewed to allow the threaded spindle to be screwed into a MacLoughlin pin (see middle diagram). Traction to the pin and counter traction to the femur (via the barrel) is applied by screwing down the angled handle as shown in the lower diagram.

The instrument is easily manipulated in a confined space and makes it possible to extract a pin from a femur as easily as a cork from a bottle.

The extractor is made in stainless steel by Charles Thackray Ltd., of Leeds.

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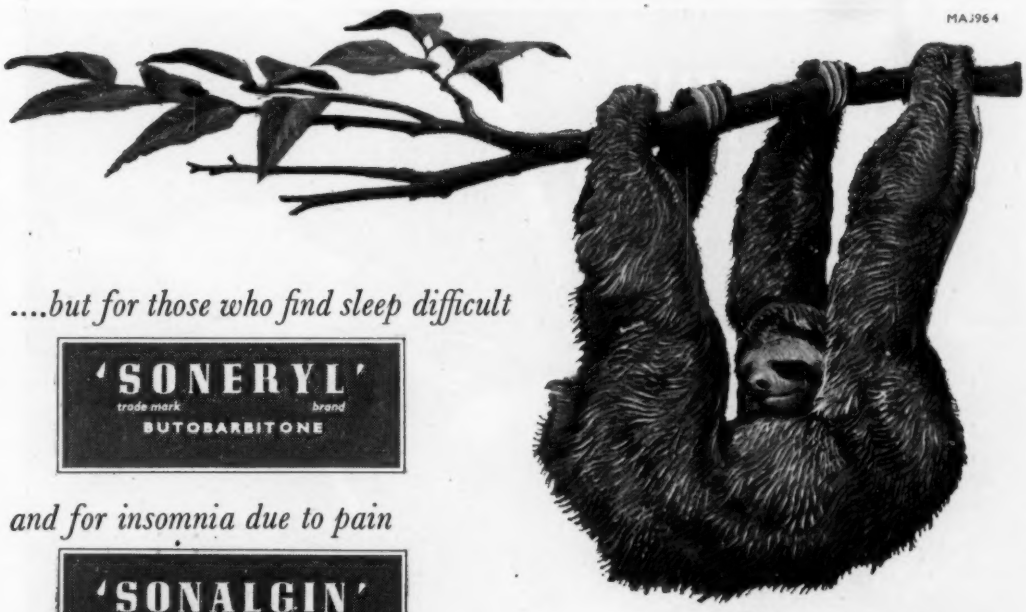

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See Lancet, July 22, 1899, p. 219

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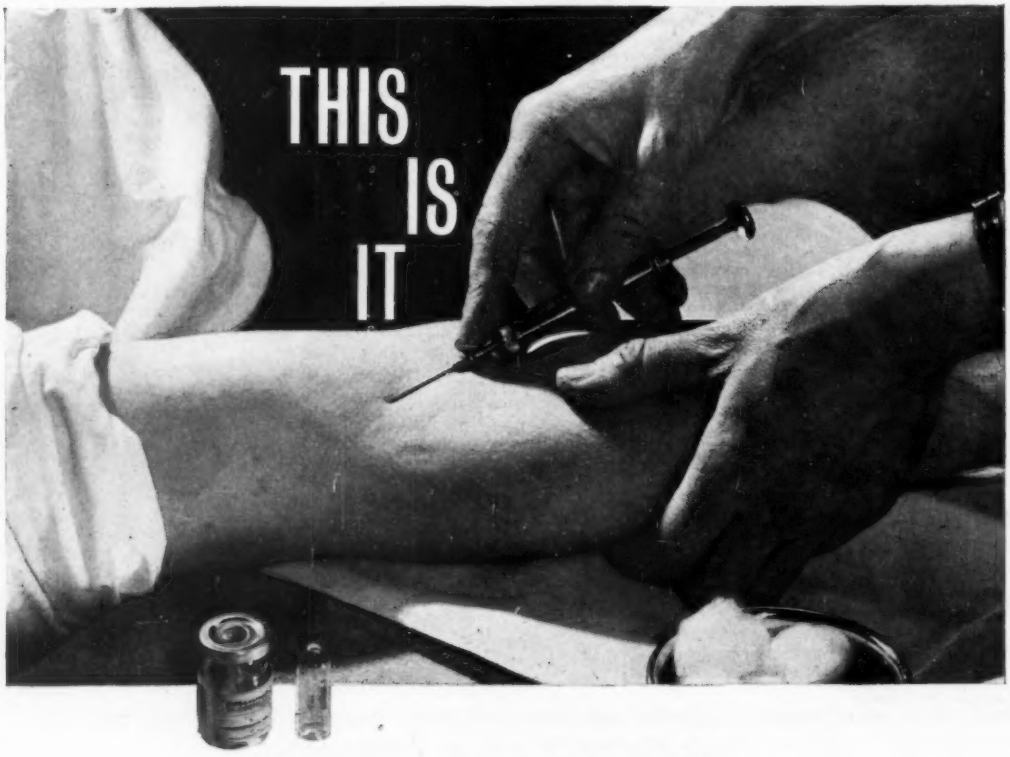

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THE LANCET

LONDON: SATURDAY, AUGUST 17, 1957

Old Bones

THE mysteries of Eleusis were nothing in comparison with those of the by-products of the meat trade. About half of a bullock goes to feed man or his pets; the skin goes to the tanner; and almost all the remainder, through channels screened from public view, is put to some useful and remunerative purpose. Drying and grinding reduce these ghastly relics to substances more or less inoffensive to sight and smell which reach the market under a variety of names, such as meal, bone meal, bone flour, meat meal, or hoof and horn. Their composition and manufacture are concealed as much by our natural squeamishness as by commercial secrecy. Some are added to vegetable feeding-stuffs for animals to give added virtue, some appear as "protein concentrates" for the same purpose, and some are applied to the land as fertilisers. The products of our native slaughter-houses are not enough for the farmers' demands and there is a large trade in animal refuse, raw and processed, imported from the far ends of the world.

That these auxiliary products of the meat trade might be the source of disease has been suspected for many years. There is little doubt that some outbreaks of foot-and-mouth disease are due to virus imported in bone-marrow, and a few years ago a considerable epidemic of anthrax was attributed to bone meal (or some similar product) incorporated in pig meal. Dr. WALKER's discovery (recounted in his article last week [1]) that members of the genus *Salmonella* are commonly contained in these materials may, therefore, not be entirely surprising, though it is certainly alarming. Salmonella infections of cattle and pigs in this country are well recognised but not common enough to be a major nuisance. Of their incidence in the lands whence we draw the raw materials for bone meal there is not much information. 9 out of 25 samples of butcher's meat in Cairo yielded salmonella, but the coincident finding of *Shigella spp.* suggests that some of these were of human origin.[2] 50% of hogs in abattoirs in Florida were found to be infected, but the proportion of infected cattle was a good deal lower.[3] About 10% of "healthy" cattle in Mexico harboured these organisms, and figures of this order have been reported from Uruguay.[4] Where herds are counted by thousands such plagues as rinderpest reduce the relative importance of salmonella infections. What is more unexpected is that salmonella can survive the processes which convert animal refuse to a dry powder: the protective action of proteinous substances has given us cause to modify many conclusions about the survival of bacteria and viruses which had been based on experiments in vitro.

It is probably too early to assess the danger to the health of man and animals from this source. The trade in imported meat products is not a new one, and it is striking that the catalogue of *Salmonella spp.* found in them contains many species isolated in this country very seldom or never. (Indeed some of the species may be new to science.) The genus *Salmonella* is pathogenic by definition [5] but not always in experience. We know that the infective dose of different species (or of different strains of one species) varies within wide limits,[6] and possibly, since the great majority of salmonella described come from sick humans or animals, the "rarity" of a species in this genus indicates a relative lack of pathogenicity rather than a smaller or more local population. It would be interesting to know the absolute numbers of these organisms in bone meal. It may be that the methods of modern bacteriology are too efficient: the proverb about "one swallow" is probably applicable to many epidemiological problems. If, on the other hand, we accept the idea that every isolation is a warning of impending danger, the use to which these products are put deserves consideration. We do not know how much of them is used as fertilisers and how much goes into feeding-stuffs. As fertilisers they cost more than double the price of the mixed inorganic fertilisers and attract no Government subsidy: their use is negligible in general farming and is almost entirely limited to the private or market garden. In any case the risk of the growing plant taking up pathogenic bacteria from the soil is remote.[7] The danger of using these substances in feeding-stuffs is more considerable. Such use is, indeed, a reasonable explanation of the sporadic salmonella infections of farm animals which are common experience, and we hope that our veterinary colleagues will pursue this line of inquiry when the opportunity arises. Nevertheless it is curious that if this risk is serious salmonella infections, especially of pigs and chickens, are not more common. The sales of compounded "rearing," "fattening," and "finishing" meal are enormous, but such figures as are available suggest that salmonella infections in these animals are less prevalent than they were twenty years ago. Dried eggs fed to pigs disseminated alien species of salmonella very rapidly. Unless the phenomenon recorded by WALKER is entirely new, we would expect to see more of these exotic species which he found in bone meal in common circulation. One other line of inquiry might be of value. There is no doubt that salmonella infection can be acquired by inhaling infective matter, and bone grinding is a dusty trade. The health of those engaged in it might give a useful hint on the risks to the general public and to our flocks and herds.

1. Walker, J. H. C. *Lancet*, Aug. 10, 1957, p. 283.
2. Floyd, T. M., Baranski, J. R., El-Gannani, M. *J. infect. Dis.* 1953, **92**, 224.
3. Galton, M. M., Smith, W. V., McElrath, H. B., Hardy, A. B. *Ibid*, 1954, **95**, 236.
4. Varela, G., Olarte, J. *J. Lab. clin. Med.* 1952, **40**, 73.
5. Kauffmann, F. Enterobacteriaceae. Copenhagen, 1951; p. 19.
6. McCullough, N. B., Eisele, C. W. *J. infect. Dis.* 1951, **88**, 278; *Ibid*, 1951, **89**, 209.
7. Rudolfs, W., Falk, L. L., Ragotzkie, R. A. *Sewage industr. Wastes*, 1951, **23**, 253.

Gamma-globulin Deficiency

IT is just twenty years since TISELIUS [1] first showed that the serum-globulins could be separated into three major components by their migratory behaviour in an electrical field. Since then a good deal has been learnt about the serum-proteins and the behaviour of the different fractions in disease. Particular interest has been shown in the slowest-moving component —the gamma fraction—because it is in this fraction that the serum antibodies are found.[2]

Congenital absence of serum-gamma-globulin was first described by BRUTON [3] in 1952 in an 8-year-old boy who had had repeated attacks of infection and who failed to show the normal antibody response to various antigens. Since then many cases have been reported and the disease has been intensively studied, especially by JANEWAY and GITLIN [4] and by GOOD.[5] It is a hereditary disorder with a sex-linked recessive inheritance occurring only in males. Gamma-globulin is probably rarely, if ever, completely absent from the serum but may be present in minute amounts which can be detected only by sensitive immunochemical techniques. Thus, whereas the range of values in normal children is 600–1300 mg. per 100 ml., in patients with "agammaglobulinæmia" values of 0–30 mg. per 100 ml. will be found.[4] These low levels are not due to excessive katabolism of the protein, as injected gamma-globulin survives for at least the normal time, having a half-life of 30 days.[5] The defect appears to be one of production, and this is associated with a remarkable absence of plasma-cells from the tissues. It is now widely accepted that antibodies are formed mainly in the plasma-cells.[6] CRAIG and GITLIN [7] have demonstrated such antibody production in healthy children by the fluorescent-antibody technique of COONS.[8] Children who were due to have repair of inguinal hernia were given subcutaneous injections of combined diphtheria, pertussis, and tetanus antigen into the thigh four days before operation. At operation an inguinal lymph-node was excised, and sections which were treated with fluorescent-labelled antibodies showed specific antibodies against diphtheria and tetanus in plasma-cells. In children with agammaglobulinæmia who had received a similar preparation, the excised lymph-nodes showed no specific antibody nor any gamma-globulin, although the administered antigenic material was easily demonstrated in the node. GOOD [5] has also shown that after intensive antigenic stimulation there is a significant rise in the number of plasma-cells in the bone-marrow and lymph-nodes of healthy people, whereas in agammaglobulinæmic children no such cells were found before or after stimulation.

These children are subject to repeated bacterial infections, but usually they are not unduly susceptible to viral infections. A few cases have been reported,[9–11] however, in which primary vaccination was followed by progressive generalised vaccinia associated with absence of normal antibody response and generally with a fatal outcome. In these patients the basic disorder may be different: one of them [9] was a female, and histological examination of her lymph-nodes showed abundant plasma-cells with few lymphocytes both in the nodes and in the peripheral blood. Although most patients with congenital agammaglobulinæmia have a normal clinical response to viral infections their immune response, measured by serum-antibody levels, is quite abnormal. Thus JANEWAY and GITLIN [4] vaccinated several children and noted that the vaccinial lesion pursued a normal course and that re-vaccination produced a typical immune response but no neutralising antibody could be detected in the serum. GOOD [5] gave repeated injections of various viral antigens into his patients both with congenital and acquired forms of the disease, and in only one instance was there any antibody response. Healthy people react to repeated intravenous injections of endotoxin from gram-negative bacteria at first with fever and rigors, but after a while they become refractory. Exactly the same response is shown by patients who lack gamma-globulin,[5] and the refractoriness would seem, therefore, to be independent of circulating antibody and to depend on some other type of immune mechanism.[12] Infections with gram-negative enteric organisms have not seemed to occur in these children; and, though this could be due to chance, it has been suggested [4] that properdin,[13] which is present in normal amounts, may be more important than antibody in resistance to such infection. Perhaps the most striking investigation which has been done is the transplantation of skin from unrelated normal donors to two children with agammaglobulinæmia.[5] In both children the grafts took, and they seem to be surviving permanently. By contrast, skin from affected children when transplanted to healthy persons was accepted initially but rejected after a few weeks. There is much recent evidence [14 15] that the acceptance or rejection of homotransplants depends on immunological factors and that the repeated failure of such transplants to survive in man, except in identical twins,[16] is due to the development of antibodies. This hypothesis is supported by these remarkable experiments.

In addition to the congenital form of agammaglobulinæmia several other conditions are known in which there is absence or severe deficiency of the protein. The serum level of gamma-globulin falls in all infants during the first few months after birth.[4] Most of the gamma-globulin found in the newborn infant's blood is derived from the mother, and the child does not begin to synthesise appreciable amounts of its own until it is a few months old. Owing to the normal katabolism of the protein the concentration falls steadily until the infant's own production provides adequate replacement. The total serum level generally falls to about 300–600 mg. per 100 ml. but occasionally it falls much lower and severe infection may then arise. It has been suggested [5] that some

1. Tiselius, A. *Biochem. J.* 1937, **311**, 313.
2. Enders, J. F. *J. clin. Invest.* 1944, **23**, 510.
3. Bruton, O. C. *Pediatrics*, 1952, **9**, 722.
4. Janeway, C. A., Gitlin, D. *Advanc. Pediat.* 1957, **9**, 65.
5. Good, R. A., Zak, S. J. *Pediatrics*, 1956, **18**, 109.
6. Fagraeus, A. *J. Immunol.* 1948, **58**, 1.
7. Craig, J. M., Gitlin, D. *Amer. J. Dis. Child.* 1954, **88**, 626.
8. Coons, A. H., Leduc, E. H., Connolly, J. M. *J. exp. Med.* 1955, **102**, 49.
9. Keidan, S. E., McCarthy, K., Haworth, J. C. *Arch. Dis. Childh.* 1953, **28**, 110.
10. Kozinn, P. J., Sigel, M. M., Gorrie, R. *Pediatrics*, 1955, **16**, 600.
11. Somers, K. *Arch. Dis. Childh.* 1957, **32**, 220.
12. Bennett, I. L. jun., Beeson, P. B. *Medicine*, 1950, **29**, 365.
13. Pillemer, L., Schoenberg, M. D., Blum, L., Wurz, L. *Science*, 1955, **122**, 545.
14. Medawar, P. B. *J. Anat., Lond.* 1944, **78**, 176.
15. Billingham, R. E., Krohn, P. L., Medawar, P. B. *Brit. med. J.* 1951, ii, 1049.
16. Merrill, J. P., Murray, J. E., Harrison, J. H., Guild, W. R. *J. Amer. med. Ass.* 1956, **160**, 277.

cases of sudden death in infancy may be due to overwhelming infection at a time when the infant's gamma-globulin level is very low. The acquired form of agammaglobulinæmia differs from the congenital in that it occurs in both sexes and it does not appear to be inherited (although an increased amount of both total globulin and gamma-globulin has been found in the healthy relatives of a few patients [17 18]). It may come on at any time from childhood to old age but usually first manifests itself in adolescence or early adult life by recurrent attacks of respiratory infection, sometimes going on to bronchiectasis.[4] Some patients have a sprue-like syndrome.[19–22] In others there is gross splenomegaly and enlargement of lymph-nodes.[17 18 23–26] Histological examination of lymphoid tissue has shown that plasma-cells are either completely absent or present only in immature forms.[18] Levels of gamma-globulin are not usually as low as in the congenital form but range from 25 to 75 mg. per 100 ml.[4] Gamma-globulin deficiency has also been reported in a wide variety of other disease conditions, including the nephrotic syndrome [27] when heavy loss occurs in the urine, amyloidosis [4] (although increased gamma-globulins are usually found in this disease), Hodgkin's disease,[28] and multiple myeloma.[17] Deficiency also occurs in various hypoproteinæmic states such as transient [29 30] or permanent [31] essential hypoproteinæmia, nutritional œdema,[32] and familial idiopathic dysproteinæmia.[33] In these disorders the gamma-globulin deficiency does not seem to be associated with undue susceptibility to infection even though the antibody response to artificial antigenic stimulation may be poor. This suggests that the enhanced susceptibility to infection in "primary" agammaglobulinæmia both of the congenital and acquired types is not due solely to the deficiency of gamma-globulin, and indeed this deficiency is probably only a manifestation of the fundamental underlying disorder which has been termed "immunological paralysis." [5]

Primary deficiency of gamma-globulin should be suspected in any patient who has very frequent bacterial infections, particularly if the same type of infection keeps recurring. The disease, however, is quite rare, and many patients who have repeated infections are found to have normal gamma-globulin levels.[34] Only three cases of the congenital form have been reported in this country, two of them in brothers.[35 36] The diagnosis is established by electrophoretic examination of the serum-proteins, and most major laboratories can now perform this. Various screening tests have been described, and one of the simplest is examination of the serum for isoagglutinins [5 22] (provided the patient's group is not AB) which will be absent or present in extremely low titre. Another simple method is the zinc-turbidity test, usually employed as a test of liver function.[37] The aim of treatment is to keep the patient relatively free from infection, and this has been achieved by the regular administration of pooled gamma-globulin. JANEWAY and GITLIN [4] recommend a dose of 0·1 g. per kg. of body-weight intramuscularly once a month, having calculated that this dose would maintain the serum level at 100–200 mg. per 100 ml. This necessitates rather a large injection (10 ml. of a 16% solution in a child weighing 30 lb.), and weekly injections might therefore be preferable. Even such a régime will not always keep the patient completely free from infection, although most severe infections will be eliminated. Not every patient will need this form of therapy, and in some the regular administration of an antibiotic will suffice.[36]

The last word has certainly not yet been said; but, although it is only five years since congenital gamma-globulin deficiency was first discovered, brilliant use of this "experiment of nature" [5] has been made by many able investigators to enlarge our understanding of protein metabolism and resistance to disease.

17. Young, I. I., Wolfson, W. Q., Cohn, C. *Amer. J. Med.* 1955, **19**, 222.
18. Citron, K. M. *Brit. med. J.* 1957, i, 1148.
19. Sanford, J. P., Favour, C. B., Tribeman, M. S. *New Engl. J. Med.* 1954, **250**, 1027.
20. Saslaw, S., Wall, R. L. *J. Lab. clin. Med.* 1954, **44**, 925.
21. Good, R. A. *Ibid*, p. 803.
22. Cooke, W. T., Weiner, W., Shinton, N. K. *Brit. med. J.* 1957, i, 1151.
23. Rohn, R. J., Behnke, R. H., Bond, W. H. *J. Lab. clin. Med.* 1954, **44**, 918.
24. Grant, G. H., Wallace, W. D. *Lancet*, 1954, ii, 671.
25. Collins, H. D., Dudley, H. R. *New Engl. J. Med.* 1955, **252**, 255.
26. Rosecan, M., Trobaugh, F. E., Danforth, W. H. *Amer. J. Med.* 1955, **19**, 303.
27. Barnett, H. L., Forman, C. W., Lavson, H. D. *Advanc. Pediat.* 1952, **5**, 53.
28. Arends, T., Coonrad, E. V., Rundles, R. W. *Amer. J. Med.* 1954, **16**, 833.
29. Hertzog, F. V., Faust, O. A. *J. Pediat.* 1950, **36**, 641.
30. Illingworth, R. S., Finch, E. *Arch. Dis. Childh.* 1954, **29**, 513.
31. Schick, B., Greenbaum, J. W. *J. Pediat.* 1945, **27**, 241.
32. Krebs, E. G. *J. Lab. clin. Med.* 1946, **31**, 85.
33. Homburger, F., Petermann, M. L. *Blood*, 1949, **4**, 1085.
34. Laurance, B. *Lancet*, 1954, ii, 873.
35. Hutchinson, J. H. *Ibid*, 1955, ii, 844.
36. Elphinstone, R. H., Wickes, I. G., Anderson, A. B. *Brit. med. J.* 1956, ii, 336.

Annotations

HYPOKALÆMIA

THE interpretation of isolated abnormalities in the plasma concentration of individual electrolytes is at present out of fashion in electrolyte studies; balance techniques and isotope estimation of total-body sodium or potassium have indicated that plasma concentration may be an inadequate or even misleading indication of excess or depletion of the common cations. Even in default of formal balance studies, emphasis has quite properly been laid on those indications of fluid and electrolyte losses and gains which can be derived from history and examination and from the estimation of urinary losses in a 24-hour specimen. Nevertheless, plasma concentrations of electrolytes can be readily and promptly estimated; and it is therefore worth reviewing their significance from time to time in the light of our growing knowledge of the natural history of electrolyte disorders. With regard to hypokalæmia, two obvious questions arise: how far does it indicate general potassium depletion? and what symptoms can be attributed to hypokalæmia per se?

The first question has lately been discussed by Scribner and Burnell.[38] Their general conclusion is that, other things being equal, the plasma-potassium level gives a good indication of the state of potassium balance; but this conclusion is considerably trenched upon by exceptions, most notably the effect of acidosis in raising the plasma-potassium and of alkalosis in lowering it. There can be no doubt of the value of a repeatedly low plasma-potassium level as a pointer to further investigation, and later repletion, of patients with chronic potassium depletion from sustained renal [39] or alimentary [40] losses. In acute states of potassium depletion, however, which are more constantly accompanied by dehydration and acidosis,

37. Kunkel, H. G. *Proc. Soc. exp. Biol., N.Y.* 1947, **66**, 217.
38. Scribner, B. H., Burnell, J. M. *Metabolism*, 1956, **5**, 468.
39. Mahler, R. F., Stanbury, S. W. *Quart. J. Med.* 1956, **25**, 21.
40. Schwartz, W. B., Relman, A. S. *J. clin. Invest.* 1953, **32**, 258.

the plasma-potassium level is quite often normal or even raised; and the absence of hypokalæmia does not exclude potassium depletion though it may make its direct treatment more difficult. In this dilemma, it is usually possible to correct dehydration and acidosis, and then reassess the plasma-potassium level; but in a few patients intravenous potassium may have to be given, in spite of a normal plasma-potassium concentration, when the evidence of potassium depletion is irrefragable and vomiting prevents oral replacement.

The symptoms "caused by" hypokalæmia have been much debated. Associated symptoms have been described in plenty, but it is not yet clear which of these are due specifically to hypokalæmia and which to intracellular potassium depletion, to disturbances of electrolytes other than potassium, or even to the general state of being ill. An interesting approach to these problems has now been described by workers in Bellet's group at Philadelphia.[41] Their starting-point was the routine analyses for serum-potassium in the clinical chemistry laboratory; in a seven-month period, 273 men (18% of men referred) and 284 woman (22%) were found to have a serum-potassium level below 3·5 m.eq. per litre. The patients with hypokalæmia had a mortality of 49%, compared with 15% in all patients admitted, in about a third of whom serum-potassium was estimated. These figures are hard to interpret because of the double selection—for admission and for electrolyte analysis—but the next stage in the investigation gives more definite information. 50 patients (20 men and 30 women) were further selected, on unspecified criteria, from the hypokalæmic patients, and were given an intravenous infusion of potassium chloride in saline or glucose, the amount depending on the initial level of serum-potassium, ranging from 21 to 60 m.eq. This amount was enough to raise the potassium concentration appreciably, but not to correct potassium depletion to any great extent; the clinical state was reassessed at this stage, and again after much larger amounts of potassium had been given, with the object of correcting the total deficit. The most commonly observed effects of correction of hypokalæmia were improved mental status (11 patients), increase of systolic blood-pressure (11), increased peristaltic activity (9), and slowing and deepening of respiration (9). Further massive administration of potassium was followed by increased alertness and muscle strength both in those who had responded and those who had not responded to the first intravenous infusion. On the other hand, in 11 patients correction of potassium depletion failed to correct muscle weakness, apathy, or poor bowel sounds, which had originally been attributed to hypokalæmia. The patients studied were suffering from a large variety of disorders, in which gastro-intestinal and hepatic diseases predominated; and the ultimate mortality in the whole group was high. Surawicz et al.[41] contrast the fairly prompt relief of mental symptoms and of bowel atony with the much more gradual improvement in the power of skeletal muscle, and suggest that this may be due to the more rapid access of intravenous potassium to brain and gut than to skeletal muscle.[42] Their paper includes a striking case-report in which paralytic ileus improved during the course of an eighty-minute infusion of 54 m.eq. of potassium with ultimate recovery.

This work adds materially to our knowledge of the symptoms which are likely to be associated with hypokalæmia and to disappear when it is corrected; but the impression remains that "specificity of the clinical manifestations of hypopotassæmia is difficult to evaluate." Perhaps the practical lesson is that correction of hypokalæmia is only a limited objective, not even a halfway house to the correction of potassium depletion; the amount of potassium to be given cannot be assessed from the plasma-potassium concentration by any convenient formula, but must be enough to correct cellular deficits as well as hypokalæmia. Occasionally, even in conditions other than hypokalæmic paralysis, simple correction of hypokalæmia may bring tangible clinical improvement; but this will be transient unless the underlying cellular depletion is also corrected.

41. Surawicz, B., Braun, H. A., Crum, W. B., Kemp, R. L., Wagner, S., Bellet, S. *Amer. J. med. Sci.* 1957, **233**, 603.
42. Black, D. A. K., Davies, H. E. F., Emery, E. W. *Lancet*, 1955, i, 1097.

RESISTANT PELVIC INFECTIONS

THE results of prompt efficient treatment of pelvic infections are usually good, but the outcome is disappointing in a few patients, especially in those not seen early in the disease and in those who have at first received inadequate antibiotic therapy. If the inflammatory process is not overcome completely, tender pelvic swellings persist, ultimately becoming fixed to surrounding tissues, and distressing symptoms may develop such as menorrhagia, pelvic pain, dysmenorrhœa, and dyspareunia. In this chronic stage patients present a problem in treatment for which hysterectomy is still all too often the only solution.

One explanation for the failure of specific therapy after inadequate or delayed antibiotic treatment is that masses of granulation-tissue are formed, in the depths of which bacteria persist sheltered from the body's defensive mechanisms and from circulating therapeutic agents. In 1952 Collins et al.[1] reported their observations on the effect of cortisone on fixed pelvic inflammatory swellings. These workers noted a greater mobility and softening of such fixed pelvic masses with some relief of symptoms after the use of this drug. Wills et al.[2] tried the combination of cortisone and tetracycline in a few patients with a long history of recurrent pelvic inflammation, and noted improvement in each of 10 cases treated; 2 of their patients, with a history of sterility following postpartum and post-abortal sepsis, became pregnant. Hurtig[3] has now described a similar method of treatment which has been in use in Ottawa since 1950. The anti-inflammatory adrenal cortical steroids and their derivatives—cortisone, hydrocortisone, prednisone, and prednisolone—are given to dissolve pelvic granulation-tissue, while specific antibiotics are administered to destroy the infecting organisms. Hurtig maintains that unless the specific antibiotic (determined by careful in-vitro sensitivity tests) is used, cortisone may have fatal consequences. He reports complete remission of symptoms, with disappearance of inflammatory masses, in each of 45 resistant cases of pelvic infection. He emphasises that no patient was given combined therapy until she had had specific antibiotic therapy for at least two weeks.

It is clear that this form of therapy could be dangerous unless care were taken to ensure that an effective antibiotic is used along with the steroids; difficulty in determining the pathogenic organism, or any doubt as to whether the organism isolated is truly the principal pathogenic agent, may make the use of this type of combined therapy hazardous. Hurtig does not think that to use a broad-spectrum antibiotic is a sufficient safeguard in this respect, though Wills et al. used one without complication in their small series. Moreover, as Hurtig points out, combined therapy is not a substitute for adequate initial antibiotic treatment, and it cannot be expected to give much benefit in chronic cases when there has been a great deal of scarring. Nevertheless these results are encouraging, and this form of therapy may be found to have real value in acute and subacute infections when the initial treatment has failed to overcome the disease completely. Once the exudative processes have become

1. Collins, C. G., Davidson, V. A., Mathews, M. M. *Med. surg. J.* 1952, **104**, 389.
2. Wills, S. H., Jacobs, W. M., Lauden, A. E. *Obstet. Gynec.* 1956, **7**, 689.
3. Hurtig, A. *Amer. J. Obstet. Gynec.* 1957, **73**, 1183.

organised and scar-tissue has formed throughout the pelvis, the patient may well be described in Hurtig's words as a "pelvic cripple"; but it seems that we may now have the means of ensuring that fewer are crippled in this way.

COLLAGEN AND CARRAGEENIN

THE major stable component of connective tissue is collagen, which provides a semi-permanent framework within which the labile cellular and intracellular elements function. The stability of collagen fibres in normal connective tissue—for example, fascia—is reflected in its slow metabolic turnover,[1] in the resistance of homotransplants to in-vivo absorption,[2] and in the indifference of collagen to treatment in vitro with tryptic enzymes. Nevertheless, physiological conditions in which collagen is rapidly removed are well known—the involution of the uterus in the puerperium is an obvious example. In rats this process leads in a few days to the loss of six-sevenths of the uterine collagen.[3] In connective-tissue diseases, too, destruction of collagen locally is often characteristic, as the subcutaneous nodules of rheumatic fever and rheumatoid arthritis consistently demonstrate.

The mechanisms of these physiological and pathological processes may differ, but they have in common the means of overcoming the resistance of collagen to absorption. They are clearly very important, but methods of study have been difficult to devise. A method lately tried involves the use of carrageenin, first suggested for the purpose by Robertson and Schwartz.[4]

Carrageenin is a sulphated polygalactose derived from Irish moss, which, injected subcutaneously into guinea-pigs, produces a granuloma rich in collagen. The biochemistry of this connective tissue at different stages in development has been studied by Jackson [5] and Slack [6]; and Williams [7] has now described the histological sequence of events in these experimental lesions. He finds that the subcutaneous mass of carrageenin is soon invaded by polymorphs and mononuclear cells which ingest the polysaccharide. By the fifth day, granulation tissue, with active fibroblasts and histiocytes, begins to invade the carrageenin mass. By the tenth day, most of the carrageenin has been ingested, leaving a highly cellular tissue interlaced with reticulin fibres which rapidly mature to collagen. But, as fibrosis overtakes the centre of the original carrageenin deposit, the recently formed peripheral collagen simultaneously disappears, and within six weeks of the outset, the whole injection site consists largely of adipose tissue.

After intradermal injection of carrageenin, the changes lead even more directly to loss of collagen. The skin of the nape of the neck in guineapigs has a thick dermal layer of dense collagen. When the carrageenin is introduced into this layer, the initial inflammatory response is soon accompanied by breakdown and resorption of collagen, detectable histologically from the fifth day, and continuing for about three weeks—that is, for as long as the polysaccharide remains localised in the dermis. The place of the original collagen is taken by adipose tissue, and the end-result is thinning of the dermal collagenous layer at the injection site. This speeding-up of the process of formation of collagen and of its subsequent loss was not found when other macromolecular substances such as methylcellulose and dextran were used instead, and Williams suggests that the high degree of sulphation of carrageenin (about 30%) may account for its specific biological effect. This degree of sulphation gives it considerable anticoagulant power, which may account for the complete absence of fibrin or fibrinoid material from the lesions, as judged by histological examination. It is possible, too, that the carrageenin might be inducing an antibody response; Arthus-type reactions, it has been claimed,[8] may lead to morphological changes in fibrils detectable by electron microscopy.

The carrageenin granuloma, then, seems to produce a type of collagen similar to that in the pregnant uterus. How this differs from the collagen of say, the fascia lata is not clear—the biochemical comparison so far shows little of significance. It might be of interest to see whether collagen formed under the carrageenin stimulus, and then excised from the site, would resist absorption when introduced as a dead homograft into a new host.

PREVENTION OF DECOMPRESSION SICKNESS

DECOMPRESSION sickness is a term used to cover caisson disease, compressed-air illness, divers' paralysis, and aero-embolism of aviators. It occurs most commonly among workers in compressed air and is usually due to too rapid decompression. The symptoms vary from slight joint pains (the bends) to paralyses, the result of air embolism in the central nervous system.[9] New regulations have been drafted[10] with the purpose of ensuring that close attention is paid to the health and safety of those working in compressed air. These regulations will apply to all work in compressed air undertaken by any commercial organisation or government department.

The proposals include one that at all times a competent person must be in attendance at the working-site to supervise operations. Where men are working in pressures exceeding 18 lb. per sq. in. air-lock attendants are obliged to keep a register of the times at which each man enters and leaves the lock, the pressures operating at these times, and the time taken to decompress each person. Other regulations cover the maximum temperatures and humidity at working sites, and there are detailed rules regarding the entrance and exit of workmen through the air-locks. Inexperienced workmen must be accompanied by an experienced compressed-air worker when entering or leaving an air-lock.

Medical supervision includes clinical examination and certification of fitness to work in compressed air by an appointed doctor, and the keeping of a compressed-air health register. New workers must be provided with advisory leaflets explaining the reasons for caution; and general hygienic facilities, such as accommodation for clothing and washing facilities, must also be provided. When the pressure in a working chamber exceeds 18 lb. per sq. in. a suitably constructed medical lock must be built at the working-site to be maintained and used solely for the purpose of treating cases of decompression sickness: it must at all times be manned by trained staff and be ready for immediate use. Labels stating that a man is a compressed-air worker must be supplied to each individual; and on the label must be written the address of the nearest medical lock.

A detailed schedule of rules for compression and decompression, together with tables to be used during such operations are also provided. The tables are to be used to calculate the rate of decompression and the time which must elapse between successive stages in lowering the pressure in the air-lock. The higher the atmospheric pressure at the start of decompression, the longer the time taken to reach normal atmospheric pressure.

These regulations are welcome. The measures necessary for preventing symptoms among workmen in this important branch of constructional engineering have been known for some time.[11] These measures have now been embodied in the new regulations, which, if properly applied, may lead to the virtual disappearance of serious caisson disease.

1. Slack, H. G. B. *Clin. Sci.* 1954, **13**, 155.
2. Glynn, L. E., Reading, C. A. Colloquium der Gesellschaft für physiologische Chemie. Berlin, 1956: p. 54.
3. Harkness, M. L. R., Harkness, R. D. *J. Physiol.* 1954, **123**, 492.
4. Robertson, W. van B., Schwartz, B. *J. biol. Chem.* 1953, **201**, 689.
5. Jackson, D. S. *Biochem. J.* 1956, **62**, 258: *Ibid*, 1956, **64**, 8P.
6. Slack, H. G. B. *Ibid*, 7P.
7. Williams, G. *J. Path. Bact.* 1957, **73**, 557.
8. Rich, A. R., Voisin, G. A., Bang, F. B. *Bull. Johns Hopk. Hosp.* 1953, **92**, 222.
9. *Lancet*, 1954, ii, 907.
10. The Work in Compressed Air Special Regulations, 1957. H.M. Stationery Office. 8*d*.
11. Paton, W. D. M., Walder, D. N. Compressed Air Illness. *Spec. Rep. Ser. med. Res. Coun., Lond.* no. 281. H.M. Stationery Office, 1954.

Public Health

ASIATIC INFLUENZA IN THE NETHERLANDS

J. MULDER
M.D.
PROFESSOR OF MEDICINE, UNIVERSITY OF LEYDEN

THREE liners from Indonesia, which disembarked in Dutch ports between the end of May and the beginning of July, had all had influenza on board. On serological and virological evidence this was Asiatic influenza. The highest attack rate on these ships (20–30%) was in the sailors who slept together in crowded rooms. From one ship, 3 children not quite recovered went ashore at the end of May. From a second ship a serologically confirmed adult case was seen acutely ill at home. In Leyden a young woman was infected by a clinical case from a ship, but so far there has been no spread there. Other confirmed cases arrived by air.

On June 14, a febrile disease appeared in a school in Bussum, near Amsterdam; within a few days 60% of a certain group of the pupils fell ill. On June 29 in the same town an institute for girls aged from 6 to 16 years was affected. 30% of the children fell ill within a day; the rest were sent home by the local doctor, and 8 became ill afterwards. Both outbreaks were confirmed as Asiastic influenza on serological and virological evidence, but the chain to Bussum from Asia could not be found.

On June 20, nearly all of the 60 inmates of an institute for disabled children in Utrecht had serologically proven Asiatic influenza. In July, a school in Rotterdam followed, and a girl aged 15 died on July 2 from virologically confirmed Asiatic influenza complicated by pneumonia due to *Staphylococcus aureus*. She may have been infected by her sister, who had a furuncle in her face. The disease was confirmed in the days following in Vlaardingen, Maassluis, and Amersfoort. The biggest focus in the general population certainly was Bussum, where many children and some adults in the town fell ill. Then a very interesting epidemiological situation developed. In Holland about 18,000 Ambonese people are voluntarily assembled in 70 crowded camps throughout the country. Between July 4 and 8 the first cases of virologically confirmed cases of Asiatic influenza started in a camp in the south of the country, and in the next four weeks it affected about 1300 of the 2400 inhabitants. Most probably this first camp was contaminated from cases among the general population in the surrounding area. From this camp the influenza was propagated very rapidly to some other camps. On Aug. 3, 40 camps had reported influenza. Many camps have 50–60% incidence of disease. There are a few cases of pneumonia, but only 1 death is reported among about 3500 cases; antibiotics contribute to this very low mortality.

There is at present no big spread in the general population of Holland. So far only 30 cases have been reported from one army unit in the south of the country (virologically confirmed).

The lesson from all this has been that a country should look at first at their crowded communities (boarding-schools, day-schools, camps) in case pandemic influenza penetrates within its borders.

CLINICAL FEATURES

The disease is extremely mild, and hard to diagnose clinically in isolated cases. Often there is only a short febrile disease lasting two to three days, with frontal headache. The fever may be high on the first or second day of the disease with initial collapse, and may relapse. One or both nasal cavities are usually obstructed. Nose bleeding is common. Conjunctivitis, cough, muscle pain and gastro-intestinal symptoms are rare. No patient has had tonsillitis.

Acute staphylococcal tracheo-bronchitis with broncho-pneumonia may complicate influenza especially when the patient himself or someone in the family has furunculosis. This may lead to death in one or two days, and we recommend penicillin treatment for patients suspected of carrying staphylococci. We recommend broad-spectrum antibiotics for influenza patients who have chronic respiratory infections or are in contact with bronchitis, for those with diabetes or heart-failure, for pregnant women, and for patients aged over 60. Patients with furunculosis should be warned to call their doctor if they get a febrile disease during the epidemic.

INVESTIGATIONS

A cytopathogenic effect in the ciliated nasal cells can help in diagnosis. The patient is asked to blow out his nose forcibly; a small wet flake of mucus is stained with methylene-blue. The degenerated and necrotic ciliated cells are easily recognised under the microscope.

The cytopathogenic effect can be sought during necropsy in the tracheal or bronchial ciliated cells. After three to four days only the basal cells are visible. To preserve the epithelium and avoid artefacts,[1] the trachea and incised lungs should be fixed in toto and pieces for histological section excised after a few days.

The isolation of the virus is extremely easy. We do not rely on garglings alone but also use nasal mucus and sputum. So far virus has been isolated from 21 of 23 specimens. We have seen 2 mild laboratory infections, though we had seen none during 20 years' work with different strains of influenza A or B.

The Asiatic virus isolated from non-pneumonic cases seems only moderately pneumotropic for mice and ferrets. Two passes from a human-egg-line and a human-ferret-line gave constant mortality in mice from virus pneumonia in the 18th and 5th passages. The virulent Liverpool A-1951 strain gave this phenomenon after 2 passages. But newly isolated strains should be tested for pneumotropy in mice, because the strains might become increasingly adapted to the animal lung and might later cause virus pneumonia in man, as (possibly) in the second wave of the 1918 epidemic.

We have found antibodies to the present Asiatic strain in people aged 80 to 90. If this were confirmed, the pandemic of 1957 might be virologically related to that of 1889–90, which also had a clear Asiatic origin but spread via Russia; perhaps today the iron curtain shapes the pathway to Europe for the virus along the deserts of the Middle East.

Since the Asiatic virus of 1957 does not overlap antigenically in surface hæmagglutinin with A-strains isolated in 1930–56, and since the human-egg-lines are insensitive to the so called β-inhibitor of normal serum, it might have an animal origin.

Without the magnificent information service set up by the World Health Organisation in Geneva under the direction of Dr. A. M.-M. Payne, we could not have made our observations so soon.

1. Hers, J. F. Ph. The Histopathology of the Respiratory Tract in Human Influenza. Leyden, 1954.

Change in Vaccination Certificate

A revised form of the international smallpox-vaccination certificate was authorised in May, 1956, but a decision of this year's World Health Assembly permits the form used in the United Kingdom to differ slightly. New forms, which can be obtained from the Ministry of Health, the Department of Health for Scotland, and the Ministry of Health and Local Government in Northern Ireland, come into general use in October, but may be used sooner. They provide space for recording a second attempt at primary vaccination where the first is unsuccessful.

INFLUENZA EPIDEMIC IN ADEN

A. L. FAWDRY
M.A., M.D. Camb.
MEDICAL OFFICER, ADEN

MANY lines of sea and air communication converge on Aden, so it was no surprise to us when Asiatic influenza reached us in the second half of June. In fact one of our medical officers had returned from Bombay on June 6 and promptly succumbed to a febrile illness with an added bronchitis, which lasted five days. On June 20 I saw during my afternoon and evening as duty medical officer a dozen outpatients with the same story of sudden fever with upper-respiratory symptoms: from that day on the epidemic gathered momentum.

By the 24th the crowd attending hospital in the morning had completely disorganised our normal outpatient arrangements: we collected them into the hospital garden, seated all the available assistant medical officers in a row under the verandah with table, chair, and stool, and tried to organise an orderly process in a queueless collection of sufferers. A fairly large proportion were employees whose need was "leave-off-work chits" just as much as medical relief. At the end of the day we broadcast a short radio talk explaining in simple terms how little, in fact, the hospital could do for this acute but short disease and emphasising the symptoms which might indicate danger and called for a doctor's attention.

From the 24th to the 29th increasing numbers of our own hospital staff reported sick until, at the peak, about half of them were off duty: fortunately the doctors and sisters were less heavily afflicted than the nursing orderlies, but the staff deficiency made it imperative to refuse admission to as many as possible of the general public with uncomplicated influenza. We cancelled all but emergency operating, and this, combined with a pronounced drop in the number of outpatients attending the surgical outpatients department, enabled us to transfer staff from theatres and X-ray departments. While things were at their height, organisation of the outpatients was made doubly difficult by the disappearance of the very helpful policemen who had been loaned to us: they too succumbed.

Other parts of the colony's medical service had their troubles: three out of three port health officers were in bed one day, and a relief doctor from Little Aden speeding to take over became a casualty from a mishap to his car. The Civil Hospital by then was recovering from its early chaos (patients were even learning to queue), so I filled the gap at the Port for the day (June 30) and thereby saw some early fatal effects of the epidemic, which occurred at that end of the town: 3 previously healthy children, aged 3, 10, and 16 years, died within forty-eight hours of the onset of fever, apparently from overwhelming toxæmia.

From July 1 onwards our sick staff began to return to duty and it was fortunate that they did, for we then began to take in patients with influenza's aftermath of respiratory complications, needing far more nursing care and medical attention than those with simple fever. Most of the deaths were of patients with frank respiratory involvement.

On July 5 the last blow to medical organisation was struck when both the lady doctors who run our maternity hospital of 60 beds succumbed at the same time, and for the first time in the hospital's history a male doctor became temporarily the obstetrician—an innovation accepted by patients and husbands with less demur than might have been expected.

By the end of the first week of July the epidemic was waning rapidly, though we were still taking in cases with varied types of pneumonia: and on July 20, a calendar month after the onset, it was to all intents and purposes finished.

CLINICAL PICTURE

The uncomplicated disease was usually of rapid onset—sometimes so rapid that a man would go to work and collapse at his job during the morning. Fever and dizziness, were the commonest complaints; there was often soreness of the throat and dry cough; also headache and generalised muscle aches. The vast majority of the sufferers were incapacitated for two days and unfit for work for three or four days. There was a small proportion with only local symptoms—sore throat, hoarseness, or cough only—and able to carry on working. There were a few who exaggerated their disability, lay down at their work, and got their friends to carry them to hospital, quasi-dying: a joke not appreciated by the friends when the patient after careful medical examination was told that he was no worse than anyone else and could walk home with his aspirin like them. One hysteric so overbreathed that he gave himself tetany. These were, of course, the exceptions, and most patients put up with their troubles stoically. (A labourer on a subsistence wage cannot be blamed for regarding the sick leave form which ensures his wages while off work as a very important document. But I think most employers of labour in the end accepted the men's word even if unsupported by doctor's signature.)

The complications noted in association with the influenza itself were few: epistaxis was fairly common; and there were a few cases of hæmatemesis in previously healthy people, probably caused by the aspirin which was our only standby for symptomatic relief on such a large scale. The temperature and humidity of the air at this time of year in Aden is such that heat hyperpyrexia certainly caused some deaths in stuffy houses without fans. The influenza hastened the deaths of some already otherwise afflicted—e.g., patients with heart-disease, tuberculosis, or asthma—and subjected others to severe strain. I admitted a boy, aged 12 years, who had been attending previously as an outpatient on account of his tuberculoid leprosy: he was febrile and sweat was pouring from those areas of his body-surface which still had a cutaneous nerve-supply: I feared his early death from hyperpyrexia, but he recovered. Several people suffered from second attacks of the uncomplicated disease.

Influenzal Pneumonia

As on previous occasions when influenza has changed its character from a sporadic to an epidemic disease, pneumonia was a dangerous and not uncommon sequel to the acute attack. Patients usually gave the history that fever had persisted for about a week instead of disappearing rapidly as in most of their friends; cough had increased and they felt so ill that they felt that they must have medical attention even if they had had none before. There were various manifestations: no single pattern emerged, and culture of sputa reflected this variety. Consolidation when seen on radiography was sometimes lobar but more often patchy and involving more than one lobe: the extent greater than physical signs would have led one to expect. Dyspnœa and toxæmia were severe: cyanosis present but hard to assess in dark-skinned patients. Hæmoptysis occurred in many without evidence of other underlying lung disease.

The available resources of our hospital, especially when partially depleted of staff and faced with an inrush, unfortunately precluded a strictly scientific approach to treatment with antibiotics. One thing was certain—that these post-influenzal pneumonias did not react as easily as do our usual lobar pneumonias to treatment. A few benefited from penicillin, but hesitantly; likewise chloramphenicol; aureomycin we finally found the most satisfactory. But even in those who reacted well to the administration of these drugs by a fall in temperature and general lessening of the toxic state, the physical and X-ray signs were slow to go.

The bacteriological findings in 25 patients' sputa were as follows:

Staphylococcus albus 3, *Staph. pyogenes* 2, hæmolytic streptococcus 0, non-hæmolytic streptococcus 14, pneumococcus 9, *Neisseria catarrhalis* 19, proteus 5, Friedländer's bacillus 4, *Hæmophilus influenzæ* 1, diphtheroids 1, *Bact. aerogenes* 1.

The paucity of infections with the hæmolytic streptococcus and *Staph. pyogenes* is remarkable, as these were considered to play the major part in the deaths after influenza in 1918 in Europe. It may well be that it reflects difference in the soil rather than the seed, as in general hæmolytic streptococci are rarely responsible for sickness and infection in this part of the world.

EPIDEMIOLOGY

Outpatient attendances were of little help in assessing the incidence in the general population as the vast majority were content to suffer at home: judging by the experience of government departments, about 50% of the inhabitants must have had the disease in the month June 20 to July 20. The colony's population is about 140,000.

The average number of deaths per week in the colony during June and July, 1956, was 42: in 1957 the deaths per week in June and the first three weeks of July numbered 49, 46, 41, 77, 128, 103, and 56. Thus it seems likely that about 200 deaths were attributable directly or indirectly to the epidemic—a case mortality of 1 in 350.

In general the incidence of the disease followed the usual pattern, reached its peak very rapidly and almost simultaneously in all branches of the civilian community in the last few days of June, and died away at the same rate.

My thanks are due to the Director of Medical Services, Aden, for permission to publish this paper.

Poliomyelitis

Concern is still felt at the high incidence of poliomyelitis this year at Coventry; up to Aug. 9, 83 cases had been confirmed, including 54 paralytic cases. About half of the 13,629 children registered for vaccination have been immunised, and there have been no confirmed cases among them. The doctors and nurses at Whitley Hospital, where most of the patients are being treated, have been vaccinated. Mr. M. Edelman, M.P., asked the Ministry of Health to send additional supplies of poliomyelitis vaccine to the city, particularly for the use of doctors and their families.[1] The Ministry replied that Coventry had had its proper share, and that, since immunity took some time to develop, vaccination would not be of much use in fighting the outbreak. A businessman offered to arrange for a gift of American vaccine to the city[2]; but the Ministry of Health would not allow the corporation to use the vaccine for its programme under the National Health Service, because Salk vaccine has not been licensed.

There are ten large areas with notification-rates this year exceeding 45 per 100,000; these include Colchester and Stevenage, with rates of over 90, but not Coventry, where the rate is about 31.

Last Friday the Ministry issued a series of questions and answers on poliomyelitis vaccine. The British vaccine, it said, was more effective and safer than Salk vaccine; if the latter were imported, safety testing would take three months. A team was going to North America to investigate the possibility of overseas manufacture of the British vaccine, and the present safety and efficacy of Salk vaccine. The import of small gifts of vaccine was being allowed because the Ministry did not wish to control individuals rigidly, as long as a doctor had taken responsibility for injection, knowing that the safety standards did not come up to British requirements. 33 such packages had been dealt with in May, 48 in June, and 58 in July. The Ministry statement makes no mention of the distinction between gifts of vaccine sent from the United States, which are permitted, and the purchase of vaccine by private persons in Britain, which is not.[3]

1. *Times*, Aug. 8, 1957.
2. *Ibid*, Aug. 9.
3. See *Lancet*, Aug. 10, 1957, p. 280.

Another point raised by Mr. Edelman was the connection between poliomyelitis and river-pollution. The Coventry health committee advises against bathing in streams and canals, though they say there is no proof of any connection between the disease and pollution of watercourses. At Gosport notices warned the public that bathing at certain states of tide might endanger health; but because no illness could be definitely traced to sewage-polluted water, these notices were withdrawn.[4] Mr. E. V. Balsom, secretary of the Institution of Public Health Engineers, said that many coast towns pumped untreated sewage into the sea, and that the cost of sewage-purification works would be huge.[5]

New notifications of poliomyelitis in England and Wales in the week ended Aug. 3 numbered 260 (260), of which 119 (123) were non-paralytic (previous week's figures in parentheses). The year's total to Aug. 3 is 2364, compared with 1485 last year and 2593 in 1950.

Conferences

CHEMICAL ADDITIVES IN FOODS

A CONFERENCE arranged jointly by the Food Law Institute of the United States, the Food Group of the Society of Chemical Industry, and the Association of Public Analysts of Great Britain was held in London on July 26.

Mr. C. W. DUNN summarised the current position of food additives in the United States, where Congress had lately begun considering amendment of the Federal Food Drug Cosmetic Act regulating the addition of chemicals to food; the Food and Drug Administration proposed that all food additives should be pre-tested for safety, and the pre-testing data properly filed before government regulation sanctioned their use, which would then be subject to a threefold review: scientific, administrative, and judicial. Mr. G. P. LARRICK and Dr. A. J. LEHMAN were both in the United States to attest before the Congress committee: their paper was presented by Mr. J. L. Harvey. The main purposes in using additives were to reduce starvation, to increase the variety of active foods, and to release women from the drudgery of the kitchen. The permitted food colours had been and were still being revised: there was no evidence that any past or present permitted colours were carcinogenic. Cancer could be produced in animals by the repeated injection of sugar, arachis oil, cottonseed oil, lard, or tannic acid: a substance could not therefore be banned from food simply because it produced any cancer in any test animal by any route of administration.

Dr. C. A. MORRELL, whose paper was presented by Dr. B. L. Oser, said that identity, or at least similarity, of control methods in various countries would be of advantage to international trade. The government had to protect public health and to maintain the consumer's confidence that his food was safe. It needed a clear and practical code of enforcement when acting as referee in instances where the interests of the public and industry seemed to vary, and this should involve a minimum of delay since it was important not to withhold from use new and desirable processes. In the first place, it was necessary to establish tolerances. A main difficulty was to define the minimum conditions which must be satisfied for the acceptance of a new substance; whatever these conditions were it was fair to acknowledge evidence for other closely related substances, and where experts disagreed on such points they and not the administrators should seek a resolution.

Mr. N. C. WRIGHT, D.SC., described the position of preservatives, colouring agents, and other chemical additives to food under the Food and Drugs Act and the procedure by which regulations made under the Act were brought into being and varied. The Food Standards

4. *Times*, Aug. 12.
5. *Ibid*, Aug. 13.

Committee, responsible jointly to the Minister of Health and the Minister of Agriculture, Fisheries, and Food, received evidence from representatives of the trade and other parties interested, and reports were published and proposals circulated to allow further representations before regulations were finally made and brought into operation.

Mr. E. J. MILLER, outlined the control of risks to operators and consumers of treated crops arising from the use of agricultural pesticides in the field and in food stores. The present desire was that control should be voluntary; apart from the general provisions of the Food and Drugs Act, legislation existed only for protection of workers using the more toxic chemicals. A voluntary scheme existed whereby manufacturers notified their intention to market new products.

Antibiotics in Food

Dr. HENRY WELCH, whose paper was presented by Mr. J. L. Harvey, said that antibiotics in animal feeding-stuffs at a level of 5–20 parts per million, or on crops, did not appear as residues in foods under normal marketing conditions; but their presence could be shown in carcases of poultry treated with higher doses. Conclusive evidence of safety and usefulness had been required in permitting the use of tetracyclines on eviscerated poultry, and would again be required if they or other antibiotics were permitted in meat or fish. To control the amount of antibiotic reaching the public through milk from cows being treated for mastitis, it was at present required that milk should be discarded for at least seventy-two hours from the final treatment. Recently three further steps had been taken: an intensive programme to educate farmers as to the importance of the problem, the publication of a notice that a warning statement would be required on the containers of antibiotic drugs for intramammary use, and the proposal of a rule to limit the penicillin content of mastitis preparations to 100,000 units per dose.

Mr. C. A. Adams presented the paper by Dr. F. S. THATCHER, who said that antibiotics should be permitted only in those foods which would normally be prepared by cooking in such a way as to destroy any residual antibiotic content. Evidence to date supported the view that in Canada the permitted levels of aureomycin (chlortetracycline) and oxytetracycline in fish and poultry (5 p.p.m. and 7 p.p.m. respectively) satisfied this criterion. Treated foods had to be clearly labelled to that effect. Any abuse of antibiotics or any attempt to extend the shelf-life of treated foods needed to be subject to strict control action by the authorities, and the use of these substances should be coupled with an increased effort to improve general standards of hygiene and sanitation. The use of antibiotics in food should be regarded as a tentative venture, final conclusions on specific aspects of sustained value and safety being possible only after experience. Each antibiotic proposed for use in this way should be considered on its own merits.

Mr. A. L. BACHARACH summarised the present legal position in Great Britain relating to the use of antibiotics. The Therapeutic Substances Act, 1956, controlled thirteen specified antibiotics in a manner designed to prevent their use by any but medical or veterinary practitioners; but three were specifically exempted from the Act if used in animal feeding-stuffs. The Preservative Regulations did not include antibiotics in the permitted list of preservatives for foods. The occurrence of small quantities of penicillin in milk from cows under veterinary treatment set a legal problem, though the amount likely to be found was considered far below the minimum sensitising or evoking doses associated with allergic responses. Such direct ill effects as had been found with antibiotics were all from relatively large and repeated doses, given almost always by injection and with therapeutic intent.

In England Now

A Running Commentary by Peripatetic Correspondents

SWEET are the uses of advertisement, and doubtless after the Egyptian Polydamna had prescribed for Helen of Troy a herb which banished all care, sorrow, and ill-humour, contemporary medical men wearied of hurling into their waste-papyrus urns the vast loads of shards, papyri, &c., advertising the Original Trojan Tranquiliser (Polydamna & Co.) ten drachma per dispensing-pack (including tax) and a drachma back on the amphora.

Modern drug-houses' circulars are even more exasperating and range from simple statements of more-or-less fact—e.g., "She thought her nappies were white until Baby drank the Detergent"—to meretricious envelopes bearing 2½*d.* stamps. I received one signed "Freddie," telling me how much he was enjoying life now that his hæmoglobin was 100%, thanks to somebody's pills. There was also a snapshot of him in a deck-chair: except that he didn't ask me for a loan, he resembled Ananias's cousin Fred, whose ideas of *meum et tuum* so far differed from those of the judge that he was given five years in which to revise them. If it is indeed Fred, any hæmoglobin he may possess he has certainly stolen and not dug out of an imaginary hæmoglobin mine in which he may try to interest you.

Alternatively of course, the deck-chair man may be a playwright at work, for many firms now employ them to write short scenarios around their medicaments. As yet I have received no script which earns my vote as the Best One-Act Play of 1957, though I enjoyed a pamphlet in which the dialogue was written all round a patient who had a large red arrow sticking in him exactly where, reasonably enough, he felt a pain. Ambroise Paré would have removed the arrow forthwith, but in these days of specialisation the G.P. had called in a consultant, presumably in toxophily. The consultant appeared on the opposite page, with a bow-tie and a hyphen, lecturing to the awestruck G.P., whose part was made up of stooge-like lines such as "By Jove, Henry, I never thought of that!"

In one of the snappier medical magazines this playwright technique is now used for a three-act quiz—a sort of *Three Characters in Search of a Diagnosis.* At the top of the bill is again our hyphenated consultant, his "feed" being usually his medical registrar. The patient is merely the excuse for the whole thing. The prologue announces that if the reader can make a diagnosis from Act I alone, he has unusual clinical acumen, luck, perspicacity, &c. (all of which I usually swap for a quick look at the answer on the back page); from Act II, common sense; and from Act III—well, you should be ashamed. But the authors don't play fair. French, H., assisted by me (I turned over the pages), once whittled down the possible causes of a patient's drowsiness to 19 differential diagnoses. Yet only at the end of Act III was I told that the patient was a product-sampler in a phenobarbitone factory.

* * *

The way a doctor takes leave of a patient is important. Who has confidence in the chap who leaves his hat on the washstand, trips over the carpet, and drives his car into the rose-bed? But it is the last sentence to the patient, the punch-line, which is the most important of all. The acute case is easy. "Have you in the office next week": "Bit of a rest, do us all good": or more facetiously: "Go easy on the grapes." The patient is left cheerful and resigned to his brief indisposition.

After my 97th visit to old Harry with his chronic chest, however, such brisk remarks fall a bit flat, and here's where the weather, skilfully used, comes in handy. Such are the vagaries of our climate that almost *any* change must be for the better. When the fogs of January turn the old boy blue, he is encouraged to look forward to the spring. The misty, moisty April gives him pneumonia, but during the district nurse's daily calls with penicillin he can look forward to summer. In July it gets so hot he can hardly breathe, so we tell him it'll be easier when it's cooler; and so we get round to where we came in.

The one week in the year when the weather is just right is a bit of a problem, but that is always the week I'm off with flu anyway.

* * *

Professor Yudkin's fascinating discovery of a relationship between television licences and coronary disease (July 27) suggests a fruitful field for further research. *What about television owners who haven't got a licence?* This may, in fact, turn out to be the answer to the entire problem. To begin with, if we steadfastly refuse to take out licences we would, I imagine, be repeatedly fined; this would put us all in lower income groups and safeguard us still more. In due course we would presumably be sent to gaol and there carry out unskilled labour with its further protective action on the coronaries. I sincerely hope that the medical profession will enter whole-heartedly (the pun is intentional) into this study. If only enough of them finish up in prison I might get that elusive consultant post, and so decrease my own chances of a coronary by 50 per cent.

* * *

The laughter of children and the click of bat on ball came through the soft summer air as the long white life-assurance form was placed on my pad at the end of a tedious evening session.

"What kind of alcoholic liquor do you consume and how much per day or per week?" "Occasionally." "I'm afraid 'occasionally' won't do." "Well, when there's a party I might drink a bit more—mind you, I'm no boozer." "Good, shall we say a party on Saturday nights—once a week?" "Oh no, I never drink on Saturday as I take the missus . . ." "Anyway once a week?" "No, I think once a week is too often. Less than that. Sometimes I never touch a drop for weeks on end." "O.K. Split the difference and say once every two weeks. Beer?" "Never touch it. Acidity. You put me off the stuff years ago." "Gin?" "I've never cared for gin. My uncle—you should remember him, doctor, he was very fond of his gin and bitters too . . . Did you say whisky, doctor? Not on your life; after that police trap . . ." "Let's get a move on. Rum?" "Taints the breath. My old woman . . ."

In desperation my left hand fished from the drawer the emergency brandy and two glasses, and to the sound of the expected response "I don't mind if I do," my right hand wrote the answer.

* * *

The Senior Partner's Daughter is to be married tomorrow and there is much bustling in our town. My wife tells me that so many of tomorrow's guests were under the hair-driers today that it was like a miniature reception. The local constabulary are diverted from crime-chasing and the resources of the Automobile Association are enlisted to ensure a smooth flow of traffic. The children's cinema matinée is extended.

Mother remains calm and her accents may be heard from time to time giving instructions about those flowers, that carpet, the awning, and the hundred-and-one other items that must not be forgotten. A taxi-driver with a dignified but rather ancient Austin is indignant when told that his machine is not suitable for conveying this bride—"but, Madam, it goes to all the best funerals."

Surgeries are cancelled for the great day, and the juniors of the other firm take over the practice and bring a no doubt welcome change to our chronics.

And where is the bride's father? He's painting the cycle rack, normally used by patients: and the most intriguing question of the day is—who will be arriving by bicycle?

* * *

One of your peripatetic correspondents is now enjoying the balmy winter sunshine (and drought, sigh my sweet-peas) of Brisbane, which is the capital of Queensland ("The Sunshine State") and a rather Lilliputian Riviera or Florida to the cool temperate parts of Australia. In outpatients here some patients refer to eructation as "bulging." Before I realised their meaning, this alarmed the psychiatrist in me with visions of a bizarre disturbance of body-image. However, after I had used the generally accepted colloquial term for this phenomenon, one patient did compromise to the extent of calling it "bulching."

Letters to the Editor

CONSULTANT AND SPECIALIST

SIR,—The letter of Dr. Rowland Hill (Aug. 10) will be generally welcomed as it clarifies the assumptions on which at least one of the profession's leaders is basing his work for the future of the medical service. May I, Sir, express a view of almost diametrical opposition?

Dr. Hill outlines the structure of the pre-N.H.S. medical service and, curiously, considers it one of "the few simple principles which should be paramount" that "the consultant . . . is a product of the machine evolved by the old . . . hospital system of the country from many generations of experience and progress" which the authorities decided "was synonymous with the highest standard of medical efficiency." This seems to be not a principle but a very simple statement of rejection of further change or progress. Apparently nine years of the National Health Service has taught Dr. Hill nothing. He has failed to notice the changed balance between central and peripheral hospitals, the change in function of much hospital work, and that so much consultant responsibility is delegated to the army of registrars that little but the form of the old system has remained.

In consequence, Dr. Hill finds it impossible that persons of mediocre attainment should stay permanently in the hospital service simply because they would like to do so. Where would Dr. Hill have them go? They are unlikely to serve the country better in a field for which they have even less training. Dr. Hill believes that the young newly appointed consultants will learn their job after appointment since "selecting the right man is more important than years of formal training." I doubt if many doctors would apply such considerations to their accountants. It seems incredible, Sir, that these can be the views of a responsible and representative member of the profession.

Apparently "consultant quality" is an eclectic and mystical quality. Surely it is nothing if not academic competence as judged by the Royal Colleges, experience, and sheer technical ability. Osler would certainly have accepted this view and it is doubtful if Hurst would have regretted additional experience at the time of his appointment. If I may quote Osler's phrase from a different context, Dr. Hill is talking of a "miasma imaginaria."

The inception of the N.H.S. has coincided with a medical revolution: a new set of techniques and the environment in which they can be utilised are growing up together. The best doctor may not be the "great man" who can carry, single-handed, the care of a complex problem, but rather he who can best harness the many technical skills and specialist opinions necessary to such a problem. Such may be the mediocre attainment of a mere technician but the necessary experience is unlikely to have been attained without the strong humanising influence of patients and a recognition of the limitations of the methods in the face of the personal factors in illness.

Dr. Hill refers to the "restraint in making new consultant posts" as the source of the present mass of trained registrars. Perhaps he can tell us whether rumour has it correctly that the Ministry of Health has rejected no single application for the creation of a new consultant appointment. Few will disagree that consultants in the future must do much of the work at present relegated to registrars. Since few consultants and few registrars are underworked, it seems that the consultant establishment will need to be increased by at least the present number of senior registrars—and presumably drawn from the same personnel.

Such a solution would be highly acceptable to present senior registrars. However, since Dr. Hill is quite clear

that older and younger consultants never have and never shall do the same work, the logic of his position is less than clear. Whether we have "young consultants," "a stooge grade of subconsultants," or security of tenure for present senior registrars, the same work will be done by the same individual doctors for the same patients with the same seniors with whom to discuss their problems. Does this involve any principles?

Can we not turn to the interests of the National Health Service (with or without capital letters) and omit the semantic confusion created by "words given to men to conceal their thoughts." Whether they are of "consultant quality" or of "mediocre attainment," the only men for the jobs are getting desperate.

May I conclude by "declaring my interests" since my decade in the registrar grades leaves me in the sordid position of, perforce, remaining anonymous. I estimate that I have conducted about 1500 outpatient clinics, have examined most of and supervised the resident staff over all of at least 10,000 inpatients, and have deputised, with full responsibility, for consultants for a total of over three years. And I hope to stay permanently in the hospital service because I would like to do so.

SENIOR REGISTRAR.

SIR,—In this imperfect world persons of only mediocre attainments are found in every profession, but Dr. Rowland Hill would forbid such of the medical quota as wish to do so from staying permanently in the hospital service. Is this not a little selfish, and does he not think that possibly some of whom he speaks have gravitated to the hospital service because they found themselves unfitted for the responsibilities of general practice? In the different atmosphere of a hospital they may do excellent work, and indeed some departments would find it almost impossible to carry on without their assistance. This was recognised in the Strachan report to which you refer, and is the experience of many working in provincial hospitals.

The permanent staff of a hospital need not be all gold. Other metals if they are solid and polished will shine and give good service.

Warwick. STEPHEN WHITTAKER.

SIR,—More than 800 senior hospital medical officers have lately asked the British Medical Association to press for payment for them on consultant scales, on the ground that they are doing consultant work. If so many feel aggrieved, something must have been seriously amiss in their original grading in 1950. All have been absolutely refused any question of personal regrading.

The grading was done by a small committee of academically minded doctors, mostly from the teaching hospitals. Professional bodies, such as the B.M.A., were not consulted. The results of this grading were not uniform; men of identical qualifications and experience were often put in different grades. Regardless of the work they were doing, few without higher qualifications were made consultants, except in certain specialties such as pathology and physical medicine.

In answer to strong protests, the grading committees (with almost the same membership) were asked to consider admitting that they had been wrong by upgrading men—moreover, against Treasury opposition. In my own region, 30–40 S.H.M.O.s were told that the committee would reconsider their cases. All of us were interviewed within an hour and a half—my own interview was occupied by finding out who I was and where I worked. Later we *all* received a multigraphed note to say that our appeals had failed.

Whether or not someone is doing consultant work is not a matter of opinion. Outpatient consultant duties imply that the doctor sees patients at the request of another doctor, without his advice being supervised. Consultant inpatient duties are defined as the unsupervised control of beds for inpatient treatment. By this definition many S.H.M.O.s are doing consultant work.

There are striking differences in grading policy between regions. Thus the proportion of S.H.M.O.s among chest specialists is high in the South-East Metropolitan Region but low in the North-West Metropolitan Region.

CUT-PRICE CONSULTANT.

SIR,—Your leading article and the article "Consultants and Senior Registrars: The Present and The Future" (June 1) merit close study for their analytical and constructive approach.

Under your heading: "Openings for Consultants" you mention the successful training to a very high standard of competence of the senior registrars, who, against the weight of exceptional competition, may not gain advancement. You reveal that it has been suggested that they may be dismissed to make place for younger men. This is the present alternative to suggesting to a man that he apply for a post at the periphery where he will get more work. He will then be used as a "pair of hands," which is the unkind term applied to a man who has stepped off the consultant ladder, to be led up the garden and sold down the river into the slavery of perpetual clinical subordination. Supported by the locals he will apply at intervals for a consultant post at his new home, to be short-listed and turned down by the casting vote of the chairman. I have never thought that regional hospitals should offer such trainee posts except as an integral part of a teaching-hospital appointment. Training for specialised clinical work is the function of the undergraduate teaching hospital and of the postgraduate specialist hospitals. There a registrar has the stimulation of daily contact with colleagues of like mind and similar or superior status, access to a library, and leisure and opportunity for study and research.

The academic function of a regional hospital is the training of house-officers. They have similar opportunity of consultation and discussion with their colleagues and may have the additional advantages of more frequent contact with their chiefs, of a wide selection and greater number of patients, and of greater clinical responsibility and operative practice under supervision. It may be thought that premature contact with the periphery may encourage in a registrar trainee hurried methods of diagnosis, precocious adventurousness, and the triumph of technique over reason. On the other hand it must be admitted that certain hospitals within the orbit of the teaching hospitals are staffed by registrars who have clinical control. These men may have less academic contact than those at regional county hospitals, where the registrar is a responsible member of a team with two or more consultants, appointed by the region with the blessing of the teaching hospitals.

Notice of a local staff vacancy brought applications from sixty candidates, fifteen of whom had the double higher qualification of fellowship and mastership of surgery. How can it be said that the unsuccessful candidates "failed to make the grade"? I can remember the primary fellowship being accepted as a higher qualification for appointment to the surgical staff of a county hospital.

"There seems at present to be no prospect of the appointment of many additional consultants." Why? Shortage of money. Because of this the proposed establishment of consultants was pruned at the start of the present service. Similarly the newly appointed lay administrators were dismissed and reappointed at a lower rate of pay. More recently regional administrative medical officers were awarded less than their due proportion of increase in salary "in the light of" rather than "in proportion to" the rise in consultants' pay. Merit awards have been "abated," public-health doctors left out, and subscriptions to professional journals and learned societies not recognised as allowable expenses for full-time men.

Less than two million pounds a year would enable all the trained senior registrars to be paid as consultants. It is surely unworthy that established consultants should fear the competition of these men in private practice. In the old days, registrars had consulting-rooms for the conduct of private practice. Senior staff was honorary and the award of merit was private practice. This money and much more could be saved by the reimposition of a ceiling on the availability under the health service of proprietary medicines, by asking patients to pay towards their maintenance while in hospital, by increasing the number of private beds while reducing the cost, and by giving the tree a good shake to dislodge the redundant lay administrative secretarial staff.

Your last suggestion of a postgraduate dean is wholly admirable. He would lead the lost sheep back to the fold and recommend suitable trainee appointments at the periphery for integration with the teaching hospitals. The chiefs would qualify for the appropriate merit award, should this quaint custom survive. His would be the magic touch to equate Dives and Lazarus. He would bring peace of mind to those workers at the periphery who for the moment would rather avoid the favourable notice of those local committees recently appointed to offer secret advice on the widening of the gap between rich and poor. Under present circumstances some of us would rather defer the receipt of any possible merit award until the Last Day.

It is now the duty of every consultant and specialist to give his mind to this problem and to search his conscience. He must decide for himself whether to take the easy course and say "You can pull the ladder up Jack, I'm in board," or whether to insist by every means in his power that our colleagues have their privileges restored and are given the status and pay which they were led to expect, which their qualifications and skill deserve, and to which the work they are now doing entitles them.

We must decide whether our interest lies in the entrenchment of established privilege or in obtaining full recognition to those on whom the future of medicine depends.

Hastings. J. A. KERR.

IMPORTATION OF POLIOMYELITIS VACCINE

SIR,—The latest reports from the U.S.A. and other countries on the effectiveness of Salk vaccine are extremely good—much better than many experts expected. However it is well to bear in mind that there are problems ahead which are as yet unsolved. Thus the difficulties of maintaining supplies of safe and effective vaccine for years to come are very great, and some of the latest American batches are deficient in antigenicity. Again the main reasons for the world-wide use of the Salk-type of vaccine are based on its effectiveness over a period of only two or three years. It is, of course, necessary to protect the community for life, and no-one knows how to set about this task. Thus it is not known whether repeated administration of the Salk-type of vaccine is the best method to use in our attempts to provide this long-term protection.

Some may think that, if the disease is suppressed for a few years, the viruses will disappear or become harmless, but it is most improbable that this could happen with polio viruses. Indeed it seems to be important that widespread alimentary-canal infection with the virus should be maintained if long-term protection is to be assured. This could, of course, be provided by feeding with attenuated strains. Further it is worth mentioning in regard to sharp local outbreaks, such as at Coventry, that although it is too late now to achieve much with the Salk-type of vaccine, feeding the population with an attenuated strain would probably arrest the outbreak completely and safely within two weeks. It is most important that such a trial should be carried out somewhere as soon as possible.

Oxford. W. RITCHIE RUSSELL.

VITAMIN SUPPLEMENTATION

SIR,—With reference to the factual article by Dr. R. M. Dykes (Aug. 3) and your annotation, may I mention a matter which is causing some disquiet? Various milk-distributing firms now sell bottled orange juice, and as this may be either delivered with milk on the doorstep or purchased from the delivery-van it is often a more convenient source of this fruit-juice than either the welfare food bottles obtained at welfare centres or the fresh fruit itself. I understand, however, that the milk-firms' orange juice contains virtually no vitamin C. While this probably matters little for the older infant or child on a mixed diet, it might prove serious for a young baby fed on a dried-milk mixture. So far I have no direct knowledge of a case of scurvy arising from this cause, but surely it is undesirable that mothers should give infants an orange juice to protect against scurvy which in fact is ineffective. Either the bottles should be labelled as unfit for infants, or ascorbic acid could be added at a later stage in preparing the juice for bottling. Fortunately there is no danger of hypervitaminosis with this vitamin, so a generous allowance of ascorbic acid could be added to allow for deterioration before consumption if this is delayed. If, as I understand, enforcement would require legislation (or could it be done by regulation?), surely the milk firms, knowing the potential danger, could be persuaded to take voluntary action? It would indeed be a stupid state of affairs if, just as milk-borne diseases are becoming rare as a result of pasteurisation and other measures, the dairy industry contributed a new hazard to health.

Institute of Child Health,
The Hospital for Sick Children,
Great Ormond Street,
London, W.C.1. ALAN MONCRIEFF.

PYRIDOXINE AND MAGNESIUM IN THE TREATMENT OF SHOCK

SIR,—Since it has recently been found that pyridoxine raises the magnesium level in the serum,[1 2] since Mg plays a vital part in all organic energy processes,[3 4] and finally since, under conditions of shock, the cell is known to give up a significant amount of this essential ion,[5–8] it is possible that all cases of shock would benefit from treatment with pyridoxine—the more so, since the cellular reabsorption of the Mg ion is known to be a relatively slow and difficult process.[3]

Patients who had been exposed to severe stress—e.g., a surgical operation or the sudden death of a near relative—and who complained of *persistent* exhaustion and asthenia, were first given control tablets for seven days and thereafter, pyridoxine in 20 mg. tablets morning and evening for a further period of seven days. They were then asked to compare the effects of the different tablets.

The following points seemed to be significant:

(*a*) There was no doubt at all in the minds of the great majority of the patients as to which of the tablets gave the better response. For example, one housewife, who "was always tired and exhausted, always wanting to sit down," was able, after one week's pyridoxine, "to do a good day's washing." Only 1 of the 19 patients treated failed to obtain a significant response and complained of nightmare and of mild headache after pyridoxine; the vitamin was withdrawn.

(*b*) Another outstanding point was the extraordinary resistance shown by some of these patients to other forms of treatment; thus 9 of these cases had tried a large variety of

1. Buscaino, V. M., Balbi, R. *Boll. Soc. ital. Biol. sper.* 1952, **28**, 113.
2. Buscaino, V. M., Balbi, R. *Acta neurol. psychiat. belg.* 1952, **7**, 1.
3. Engbaek, L. *Pharmacol. Rev.* 1952, **44**, 396.
4. Perry, S. V. *Physiol. Rev.* 1956, **36**, 1.
5. Root, W. S., Allison, J. B., Cole, W. H., Holmes, J. H., Walcott, W. W. *Amer. J. Physiol.* 1947, **149**, 52.
6. Beecher, H. K., Simeone, F. A., Burnett, C. H., Shapiro, S. I., Sullivan, E. R., Mallory, T. B. *Surgery*, 1947, **22**, 672.
7. Brown, R. W. *J. Kans. med. Soc.* 1956, **57**, 170.
8. Kimura, K., Hara, R., Iijima, N. *J. pharm. Soc., Japan*, 1952, **73**, 1240.

"tonics" over periods varying from five months to ten years, all with little or no response. It was not surprising therefore, that the response obtained with the control tablets was poor. This apparent resistance to treatment and slow recovery, noted in these 9 patients, brings to mind the fact already mentioned —namely, that the cell membrane is relatively impermeable to Mg.

(c) The possibility of using Mg, and therefore pyridoxine, as a therapeutic agent, was first suggested by the fact that three of the patients listed seemed to show some improvement whilst taking pulv. mag. trisil. co.

The available evidence seems to suggest that pyridoxine's control of Mg metabolism may be in part responsible for these findings.

I have pleasure in acknowledging a generous supply of pyridoxine donated by Roche Products Ltd. for the purposes of this investigation.

Dundee. J. C. ANNAND.

TESTOSTERONE THERAPY IN STUNTED CHILDREN

SIR,—Your excellent annotation [1] finished with the sentence: "At present no effective preparation of growth-hormone is available; and while we wait for it, we should evidently avoid substitutes that do more harm than good." This was of great and timely value to the profession. Because the annotation was otherwise so interesting I would like to suggest, however, that there is one very ambiguous sentence: "Sobel et al. now show that methyltestosterone 5 mg. a day by mouth for six months accelerates bony development though without closing the epiphyses." Perhaps the meaning is not quite clear.

"Bony development" basically consists in cartilage growth (and thus lengthening of the bones and increase in height) and ossification as an end-point. When ossification (and this includes of course closure of epiphyses) is complete, bone growth or development has ceased. Therefore, as you accelerate bony development you will at the same time accelerate the *timing* of closure of epiphyses. This was the whole point of the observations of Sobel and her co-workers. In a word, there was less time for growing-in before the epiphyses closed.

Child Development Unit, Department of Pediatrics, University of Louisville School of Medicine, Louisville, Kentucky, U.S.A. FRANK FALKNER.

STEATORRHŒA AND HYPOPARATHYROIDISM

SIR,—Dr. Jackson (July 6) says that he only attempted to point out the coincidence of steatorrhœa and hypoparathyroidism, without discriminating between primary, secondary, and pseudo. But in all the cases reviewed by him there was a combination of low serum-calcium and high serum-phosphorus, characteristic of primary hypoparathyroidism, and in one case no parathyroid tissue was found at necropsy. In all but one of our cases of steatorrhœa in which we found a low serum-calcium, the serum-phosphorus was never above the normal level and was often very low. In one of these cases with low calcium and phosphorus we found at necropsy that the parathyroid glands were small, but perfectly normal microscopically. They had not responded to their normal stimulus—a low serum-calcium.

In one of our cases [2] mentioned by Dr. Jackson, the serum-phosphorus was high, and we said expressly that this case was not included in our series of secondary hypoparathyroidism but was a case of primary hypofunction of the glands with co-existing steatorrhœa. In this case, as in the cases reviewed by Dr. Jackson, the drop in serum-calcium was *primary*, due to a hypofunction of the parathyroids, whereas in the cases with secondary hypoparathyroidism the decrease in serum-calcium was due to the steatorrhœa, and the hypofunction of the gland manifested itself in the failure to raise the serum-calcium.

I think Dr. Jackson is right in drawing attention to the syndrome of primary (or idiopathic) hypoparathyroidism and co-existing steatorrhœa, which needs further study. I hope Dr. Nordin also will regard this as an answer to his letter in the same issue.

University Medical Clinic B, Rikshospitalet, Oslo, Norway. H. A. SALVESEN.

1. *Lancet*, 1957, i, 1341.
2. Salvesen, H. A., Böe, J. *Acta endocr., Kbh.* 1953, **14**, 215.

THE CHILD'S RIGHT TO ADOPTION

SIR,—I have just seen Dr. Burbury's letter (June 29), and would comment on the last paragraph. Dr. Burbury says that "it seems to be assumed" that all would-be adopters have "good" reasons for wanting to adopt. But assumed by whom? Certainly not by adoption workers of any kind, whose duty it is to assess the motives of applicants. So far as adoption societies are concerned (and it is my special task here to speak on their behalf) it is simply not true that less care is taken to find children satisfactory parents than to find adopters satisfactory children. The child comes first, and with the present great preponderance of people wanting to adopt over children needing adoption, it is possible to be extremely selective in the choice of adopters. Adoption societies may, of course, make a mistake in placing sometimes; and it is the occasional failure that the psychiatrist sees and, apparently uses as the basis for a judgment on adoption societies' work as a whole.

MARGARET KORNITZER
Hon. press officer, Standing Conference of Societies Registered for Adoption.
Bromley, Kent.

ATHEROSCLEROSIS IN THE BANTU

SIR,—While we are in accord with Dr. Woods and Dr. Laurie (May 25) in denying that the Bantu is "relatively free from atherosclerosis," it is our opinion that differences may exist in the severity or quality of the disease between the Bantu and white races of Europe and North America. In any discussion on this subject, there is the implicit assumption that reference is specifically made to the systemic arteries in general, although changes in the cerebral and coronary arteries do not necessarily parallel those in the aorta. From subjective studies at this hospital we have the impression that in the older age-groups severe degrees of aortic and coronary atherosclerosis are less common in the Bantu than in white subjects.[1]

In further studies in association with our colleague Dr. A. R. P. Walker, of the South African Institute for Medical Research, changes in the chemical composition and the degree of atherosclerosis in the aorta in various age-groups have been investigated. It has been found that the increases in the dry weight of the ash, calcium, phosphate, total fat, cholesterol, and phospholipid and a decrease in elastin are more marked with increasing age in white as compared to Bantu South African subjects.[2] Only in respect to collagen is the percentage composition unaffected by age in both races. The changes, however, only become significant in the over-40 age-groups. It would appear, however, that the differences in the severity of the atherosclerotic lesions in the aorta are less striking than the rarity of coronary thrombosis in Bantu subjects as compared to white subjects would lead us to expect. This observation emphasises the necessity for investigation of other causative factors in the pathogenesis of thrombosis. Nevertheless, coronary thrombosis seldom develops in the absence of coronary atherosclerosis and we feel that it is unwise to assume as yet that the low incidence of coronary thrombosis and the lesser degrees of atherosclerosis in the coronary and

1. Higginson, J., Pepler, W. J. *J. clin. Invest.* 1954, **33**, 1366.
2. Annual Report, South African Institute for Medical Research, 1956, **15**.

systemic arteries of the Bantu are only coincidental. Our view is best summarised in the statement that the Bantu would appear to be relatively free from the complications which are generally believed to be the result of severe atherosclerosis.

Department of Medicine, Baragwanath Hospital, Johannesburg. K. J. KEELEY.

Geographical Pathology Unit, South African Institute for Medical Research, Johannesburg. J. HIGGINSON.

ENDOCRINE TRANSPLANTATION

SIR,—Those who have worked on the homotransplantation of endocrine glands will endorse the cautious tone of your annotation (July 27), for the extensive literature of the subject is largely a record of failure. There is, however, evidence not quoted in your review which suggests that homografts of neonatal endocrine glands are more likely to be successful than grafts obtained from adults.

Ingle et al.,[1] for instance, removed the adrenals of 26 adult rats and inserted into the rats adrenal grafts from a different strain of adult rats. No successful grafts resulted, though the same technique was highly successful when grafts were exchanged between siblings. On the other hand, Higgins and Ingle [2] found that of 21 adult adrenalectomised rats who received an adrenal implant from an unrelated newborn donor, 9 survived with a functioning graft. In these experiments the rats, though unrelated, were of the same laboratory strain and the behaviour of the survivors was not followed for more than four months. I carried this work a step further [3] by studying the survivors over long periods, and by using rats of different strains; the final results of this experiment can now be given.

103 adult albino rats were the hosts. The adrenal grafts came from rats within seventy-two hours of birth who had been bred in a laboratory different to that supplying the host strain of rats. The hosts had both adrenals removed and the neonatal adrenal graft inserted at the same operation. They drank saline solution instead of water for two weeks after operation, but had no other special treatment. Three sites of implantation were used—the surface of erector spinæ, a wound in the muscle belly of erector spinæ, and the femoral perivascular sheath—and all yielded approximately equal results.

29 successful adrenal grafts were obtained in the 103 hosts. Inspection of these grafts showed a well-encapsulated nodule of tissue with an obvious adventitious blood-supply. Growth in size began at the end of the first month and continued into the fourth month, when it stabilised at a size a little less than that of 2 adult adrenals. 5 of the grafts were excised in the first and second months, and these showed healthy adrenal cortical tissue on section: these animals died within the next month. In the remaining animals the grafts were inspected and photographed at intervals and the graft excised at death or when the survivors were killed at the end of the experiment. All these 24 animals lived for three months, 16 for more than six months, 11 for more than a year, and 3 for eighteen, twenty, and twenty-one months after grafting. Adrenal cortical tissue was demonstrated at the graft site in all these animals. No accessory or residual adrenal cortical tissue was found at necropsy in any of these survivors, though a number of other animals with unsuccessful grafts survived for some months on accessory tissue.

The significance of these results lies in the fact that these grafts were made between rats of different laboratory strains. That rodents are fairly receptive to endocrine homografts has often been shown, but when precautions are taken to eliminate a blood-relationship between donor and host then successful grafts of adult endocrine tissue become uncommon. This was clearly shown by Ingle and Higgins,[4] and in a series of exchanges of adult adrenals between rats from different laboratories I found only 1 successful graft in 14 exchanges.

From these figures I believe it is right to conclude that it is easier to make endocrine homografts when embryonic rather than adult grafts are used. Nevertheless, there is no certainty as yet that any given graft will succeed, for only a third of the grafts in my series were effective. It also appears that a few of these grafts will cease to function after a period of normal working.

It may well be that many of these free grafts die from failure to receive adequate nourishment in the first few critical days when they are dependent on tissue fluid for their nutrition and before an adventitious circulation has developed. This gives a particular interest to the work of Sterling and Goldsmith.[5]

A woman, aged 29, had exceptionally severe postoperative hypoparathyroidism of ten years' standing, requiring daily medical attention. She was treated by the implantation of the thyroid and parathyroid glands of a baby of 21 days who had died after an operation. The glands were removed in a block along with the carotid arteries and jugular veins, and a direct vascular anastomosis was made with the superficial epigastric vessels within two hours of the death of the baby. The gland was seen to change colour on release of the clamps. At the end of the second year this woman needed no specific therapy and her blood chemistry was normal. It may be that the use of vascular anastomosis may reduce one of the hazards to which free endocrine grafts are exposed.

Taken together, I believe that these reports provide a little encouragement to those seeking a method of endocrine homotransplantation. This field of work is under the influence of many known and unknown factors and conclusions must be tentative.

There are now relatively few cases of endocrine deficiency in which medical replacement therapy is unsuccessful, but an occasional patient is seen in whom an endocrine homograft might be helpful. There is no justification for believing that a graft of adult tissue is likely to succeed, and disquiet must be felt over the use of neoplastic tissue. I believe that the evidence quoted here makes it reasonable to consider the grafting of embryonic endocrine material.

Middlesex Hospital, London. P. F. JONES.

GASTRIC ULCER AND ABO BLOOD-GROUPS

SIR,—The paper by Dr. Balme and Dr. Jennings [6] appears to confirm the suggestion that the relationship between ABO blood-groups and gastric diseases is concerned with intragastric site, despite the provocative remarks of Dr. Wiener in your columns last year.[7] Although their female cases are few in number, they fail to show an association between group O and mid-gastric lesions—that is, in the area occupied by the fundic glands. In a recently completed retrospective study of chronic gastric ulcer from four teaching hospitals in Sydney, which includes 430 female cases, there does appear to be an equal association between blood-group O and ulcers in the fundic region in both sexes. There is, however, a sex difference in the sites affected, there being a significantly higher proportion of ulcers in the fundic region in women. This is also shown in Balme and Jennings's figures.

It seems curious that although Ihre and Müller [8] first pointed out this sex difference in 1943, the knowledge does not appear to have been assimilated into the folk-lore of the disease. In the face of both blood-group and sex differences affecting the intragastric localisation of chronic gastric ulcers, one might wonder whether we are justified in considering chronic gastric ulcer as a single or uniform disease from an ætiological point of view.

Sydney Hospital, Sydney, New South Wales. B. P. BILLINGTON.

1. Ingle, D. J., Higgins, G. M., Nilson, H. W. *Amer. J. Physiol.* 1938, **121**, 650.
2. Higgins, G. M., Ingle, D. J. *Proc. Mayo Clin.* 1937, **12**, 69.
3. Jones, P. F. *In* Ciba Foundation Symposium on Preservation and Transplantation of Normal Tissues. London, 1954; p. 110.
4. Ingle, D. J., Higgins, G. M. *Proc. Soc. exp. Biol., N.Y.* 1938, **39**, 165.
5. Sterling, J. A., Goldsmith, R. *Surgery*, 1954, **35**, 624; *Surg. Forum, Chicago*, 1955, **5**, 603.
6. Balme, R. H., Jennings, D. *Lancet*, 1957, **i**, 1219.
7. Wiener, A. S. *Ibid*, 1956, **ii**, 1308.
8. Ihre, B. J. E., Müller, R. *Acta med. scand.* 1943, **116**, 33.

A NEW DISEASE?

SIR,—Harry Hawke's ingenious and witty contribution to the Widdicombe File is marred by a misprint. Frascatorius's shepherd was not called Syphilis (that name being always confined to the disease) but Syphilus. The key passage describing the naming of the disease runs as follows [1]:

"Syphilus estendit turpes per corpus achores
Insomnes primus noctes convulsaque membra
Sensit, et a primo traxit cognomine morbus
Syphilidenque ab eo labem dixere coloni."

Sunderland. R. E. IRVINE.

COST OF ESTIMATING SERUM-TRANSAMINASE

SIR,—The report by Dr. Phear and Dr. Stirland (Aug. 10) on the value of estimating fibrinogen and C-reactive protein levels in myocardial infarction is most welcome. These tests may or may not be more valuable than the estimation of the level of glutamic-oxalacetic transaminase in the serum, but not because "apparatus for this estimation is costly and is available in only a few laboratories." It is true that one technique based on the measurement of reduced coenzyme requires an ultraviolet spectrophotometer and expensive enzymatic reagents.[2] However, another method [3] requires no enzymatic reagents and can be carried out in any laboratory which possesses a balance, a centrifuge, and a colorimeter.

Though the authors measured their colour at "490 mμ" which can only be done with a spectrophotometer, we have found that reliable results can be obtained with an ordinary photoelectric colorimeter using a green filter. The reagents are prepared easily or can be purchased ready-made from the Standard Scientific Supply Corporation of New York. Whereas with the measurement of reduced coenzyme only one estimation can be carried out at a time, the second method of Wroblewski and his colleagues allows any number of tests to be carried out simultaneously—as in the estimation of the serum-phosphatase.

A modification which does not even require centrifugation has been published in a prospectus issued by the Sigma Chemical Company of St. Louis. Unhappily the exact composition of the reagents (obtainable in this country from George T. Gurr Ltd.) is not disclosed.

St. Bartholomew's Hospital, London, E.C.1. H. LEHMANN
E. RYAN.

UNUSED CHILDREN'S BEDS IN HOSPITALS

SIR,—A peripatetic correspondent pointed out last week that in hospitals throughout the country children's beds are becoming redundant. If this is so then I can suggest an immediate remedy which would be of inestimable benefit to child patients and pædiatricians alike. It would also save pædiatricians from any cynical aspersions about inventing new diseases to keep themselves busy.

Let the pædiatricians apply themselves seriously to the problem of "mentally defective" children. Let us have no more diagnoses of "mental deficiency" in children and, following that, complete apathy about their future treatment. We have seen some very small beginnings recently, but the plain facts are that until all doctors believe in the physical basis of mental deficiency and are prepared to unravel it we shall get nowhere.

It is a catastrophe that, so far as children are concerned, mental-deficiency practice ever became allied to psychological medicine. Time after time one hears of doctors saying, "Nothing can be done. He's a mental case. Put him in an institution!" They honestly believe that the cause of the child's condition is some form of mental disorder.

There are a host of biochemical disorders yet to be solved and endless work to be done on brain-injured children. Even at a very simple everyday level, there is no reason at all why many more backward children should not be investigated and cared for in pædiatric wards. May the day soon come when all such children will be fully accepted for pædiatric, not psychiatric, care.

Chertsey, Surrey. J. M. CRAWFORD.

THE BEHAVIOUR OF INHALED GRASS INFLORESCENCES

SIR,—Dr. Godfrey's article last week on this clinical rarity calls to mind a boy of about six years under my care several years ago.

After a few days with a clinical and radiological diagnosis of right basal pneumonia, he developed a small subcutaneous abscess in the back, over the right lower ribs. A day or so after incision I was asked to inspect some hairs protruding from the wound, and these proved to arise from a complete barley grass inflorescence 4 cm. long. His recovery was uneventful. The mother then recalled that some two or three months previously, after sucking some grass, the child had a violent attack of coughing.

The similarity to Dr. Godfrey's second case seemed so complete as to merit brief comment.

Lincoln. E. P. MORLEY.

THE UNEXAMINED PATIENT

SIR,—The letter by "Surgeon" in your issue of Aug. 3 is rather timely, but why blame the overburdened general practitioner when the same thing is constantly happening throughout the whole hospital service.

On a recent occasion, a man with "? lumbar spine" was referred to the hospital by the general practitioner. His history was taken by the hospital registrar, and then the patient was seen by the surgeon. When he arrived at the X-ray department, he was told to go into a cubicle and get undressed. With rather a wry smile he said "Thanks, Sister, you are the first person so far who has asked me to take my coat off." To say that an episode such as this was "by no means unusual" would be an understatement. It would be more correct to say that it was quite common.

RADIOLOGIST.

MECHANICAL FACTORS IN ATHEROSCLEROSIS

SIR,—I was interested in Professor Duguid's latest report [1] on the ætiology of atherosclerosis, and in particular in the importance he now seems to place on intimal hæmorrhage in the origin of the lipid in atherosclerotic plaques. I would like, however, to correct his historical account of the description of intimal hæmorrhage. He states that "special attention has been given to it (intimal hæmorrhage) in recent years, chiefly as a result of the detailed studies by Winternitz et al. (1938), Paterson (1938), and Wartman (1938)." This list of references should read "Paterson (1936 and 1938), Winternitz et al. (1937 and 1938) and Wartman (1938)." The first detailed description of intimal hæmorrhage as we now know it, and its origin from the rupture of intimal capillaries, was made by Paterson [2] while he was working in the department of pathology of the University of Toronto under the direction of the late Prof. Oskar Klotz. Winternitz et al. published their first paper on the subject in the *American Heart Journal*,[3] and their well-known monograph in 1938. I am bringing this matter to your attention in fairness to Dr. Paterson, and because his original report came from this department.

Department of Pathology, University of Toronto. JOHN HAMILTON.

1. Frascatorius, H. Syphilis. 1530. Book 3, lines 335–8.
2. Karmen, A., Wroblewski, F., La Due, J. S. *J. clin. Invest.* 1955, **34**, 126.
3. Cabaud, P., Leeper, R., Wroblewski, F. *Amer. J. clin. Path.* 1956, **26**, 1101.

1. Duguid, J. B., Robertson, W. B. *Lancet*, 1957, **i**, 1205.
2. *Arch. Path.* 1936, **22**, 313.
3. *Amer. Heart J.* 1937, **14**, 399.

NEUTRALISATION OF CANINE-DISTEMPER VIRUS BY SERUM OF PATIENTS CONVALESCENT FROM MEASLES

SIR,—The question of whether canine-distemper virus (C.D.V.) may produce illness in man has been much discussed.

Adams [1] found clinical and serological evidence indicating a possible immunological relationship between canine distemper and a respiratory disease in children. Adams and Imagawa [2] suggested a possible relationship between distemper and measles. The similar pathological findings in the two diseases were emphasised, and evidence was reported of cross-neutralisation in low titre.

Karzon [3] studied a neutralising antibody against C.D.V. found in man. The neutralising substance was transmitted via the placenta from the mother to the fœtus. It was lost by the 6th month, and reappeared in the population between the 2nd and 10th years of life. It reached an incidence of almost 100% in adults.

I reported corresponding findings last year.[4] Using a neutralisation-test technique by intracerebral inoculation in baby mice, I examined serum samples from adults and from children of different ages for C.D.V.-neutralising capacity. The serological responses, charted by age-groups, gave a curve resembling the typical immune response to common viral infections in man (see figure).

Attempts were made to find a relationship between illness in man and the appearance of C.D.V.-neutralising activity in human sera. Initially paired acute and convalescent sera were tested from children treated in Karolinska Sjukhuset in 1954 and 1955 for various acute infectious diseases. The capacity of C.D.V.-neutralisation was not acquired during the illness by any of the patients investigated, but since the case-material originated in a pædiatric clinic, where children with epidemic diseases were not admitted, the range of infectious diseases was limited. When the age-distribution of C.D.V.-neutralising substances was found to resemble the typical curve of immune response to common human viral infections, attempts were made to study the most common epidemic infections of childhood.

Retrospective analysis of the histories of previously investigated patients, all aged 6 months to 15 years, showed no relationship of C.D.V.-neutralising activity to past infections with mumps, chickenpox, exanthem subitum, German measles, infectious mononucleosis, or infectious hepatitis. But there was an evident relationship with measles:

	No. of patients	*C.D.V.-neutralising capacity Found*	*Not found*
History of measles ..	38	37	1
No history of measles ..	78	13	65

In March, 1957, there was an outbreak of measles in Stockholm. Paired acute and convalescent sera from measles patients were kindly provided through the courtesy of Dr. J. Ström, Epidemisjukhuset, Stockholm. 14 patients were investigated—2 adults and 12 children, $1^1/_2$ to 13 years old, admitted to the hospital for infectious diseases with clinically typical measles. Acute serum was collected three to eight days after onset of symptoms and convalescent serum eleven to thirty-five days after the onset. No treatment with gamma-globulin or blood-transfusions was given during the illness.

By use of the neutralisation-test technique previously outlined,[4] serum or serum dilutions, heated to 56°C for thirty minutes, were tested against an equal volume of mouse-adapted C.D.V. The amount of virus used was just sufficient to cause almost uniformly 100% mortality in the test mice. The serum-virus mixtures were kept at room-temperature for thirty minutes before intracerebral inoculation into mice aged 24–48 hours. Acute and convalescent sera from the same patient were tested simultaneously.

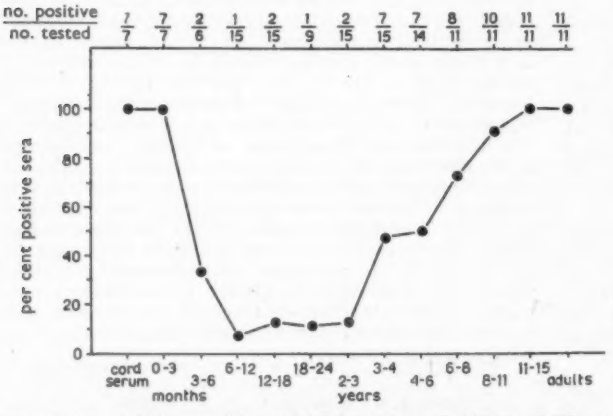
In 11 of the 14 patients studied, I found at least a fourfold rise in C.D.V.-neutralising titre from the acute to the convalescent phase—a rise which can be considered significant. In 3 other cases there was a rise which was not significant. C.D.V.-neutralising antibodies appeared on the third to seventh day after the onset of measles. End-point titrations of convalescent sera have yet not been completed, but so far a considerable variation has been found in titres in different patients, ranging from 1 : 5 to at least 1 : 625.

These preliminary studies will be continued. Further investigations will be needed before it can be settled whether measles and distemper are caused by an identical agent or by separate agents possessing common antigenic structures.

Department of Virus Research, Karolinska Institutet, School of Medicine, State Bacteriological Laboratory, and Pædiatric Clinic, Karolinska Sjukhuset, Stockholm.

GUN CARLSTRÖM.

1. Adams, J. M. *Pediatrics*, 1953, **11**, 15.
2. Adams, J. M., Imagawa, D. T. *Ped. Clin. N. Amer.* 1957, p. 193.
3. Karzon, D. T. *Pediatrics*, 1955, **16**, 809.
4. Carlström, G. *Acta Pædiat.* 1956, **45**, 180.



Distribution of CDV-neutralising activity in adults and children of different ages. (The serological responses are given by age-groups.)

MONGOLISM AND OTHER CONGENITAL ABNORMALITIES

SIR,—I have long been interested in the cause of mongolism and its spread throughout the world. I cannot agree with Dr. Pleydell's conclusions.[1]

It is odd that no sharp-witted medical man nor any attentive artist ever put down the real image of a mongol before Séguin,[2] followed by Langdon-Down,[3] Fraser,[4] and Mitchell.[5] The frequency of mongolism seems to be steadily increasing. Bleyer in 1932 [6] found 1–2 mongols per 1000 births in the U.S.A., but Beidlman in 1945 [7] found 3·4 per 1000. Professor van der Scheer, in 1916–19,[8] gave the following figures: 7 million inhabitants and 384 living mongols in the Netherlands. In 1942 van Voorthuysen [9] found per 9 million inhabitants 1224 living mongols. The number of psychotic patients cared for in institutes doubled from 1919 to 1942, but the number of mongols *trebled*.

Another interesting point is the difference in prevalence in several countries. It is highest in Finland [10] while in Indonesia neither I nor other people found a single case in 16 years' experience

1. Pleydell, M. J. *Lancet*, 1957, i, 1314.
2. Séguin, E. Traitement moral, Hygiène et Education des Idiots. Paris, 1843.
3. Down, J. L. *Lond. Hosp. Rep.* 1866, **3**, 259.
4. Fraser, J. *J. Ment. Sci.* 1876, **98**, 169.
5. Mitchell, A. *Ibid*, p. 174.
6. Bleyer, A. *Amer. J. Dis. Child.* 1932, **44**, 503.
7. Beidlman, B. *Amer. J. ment. Defic.* 1945, **50**, 35.
8. van der Scheer, W. M. Beitrage zur Kenntniss der mongoloide Missbildung. Berlin, 1927.
9. van Voorthuysen, A. *Tijdschr. Buitengew. Onderwys*, 1943.
10. Lahdensuu, S. *Acta. pædiat., Stockh.* 1937, **21**, 256.

amongst pure-bred Javanese, Ambonese, and Madurese before 1942. The same seemed to be true of French Equatorial Africa and the West Indies for thoroughbred Negroes and Indians. During my residence in Iraq I found a great number of mongols amongst the Arab population.

What is the cause of the congenital malformation called mongolism: a hereditary trait, evidenced by the examination of twins, or an arrest of the early fœtal development (Bolk's[11] fœtalisation theory) of unknown cause? Parental abuse of alcohol, venereal disease, blood-group antagonisms, and viral infections in the very early weeks of pregnancy have been accused and later acquitted as real causes. Personal inquiries in families with mongols lead me to emphasise "les petits signes mongoliens" (e.g., slanting eyes, deformities of the ear, camptodactyly, and muscular and articular hypotonicity &c.) in the ancestors. Though one mongol in the family seems the rule, two cases have been seen and I know one family with three mongols; both parents presented a great number of "petits signes mongoliens" with a good intellectual state.

Once I thought there was a real increase in the number of mongols in a certain place where at the same time a large number of school-children presented a non-toxic goitre caused by iodide-poor water. Years later the average shifted again to a more normal number; but the prevalence of non-toxic goitres did not diminish so rapidly.

Dr. Pleydell's article would be more valuable if he gave details of the number of children in the families with a mongol, the birth number, the average maternal age when conceiving a mongol, the degree of inbreeding, the result of the clinical examination of father, mother, other children, and relatives, and the nutritional condition of the Northamptonshire population.

Experienced Dutch teachers of pædiatrics insist that the prevalence of congenital heart-disease is lower among mongols: nowadays it is about 25–30%. Ostium atrioventriculare persistens is the most characteristic lesion, but non-cyanotic defects such as the "maladie de Roger" are commoner. Hare-lip, cleft palate, spina bifida, and anencephaly are often seen as symptoms of the "status dysraphicus" which may be associated with mongolism without having anything in common as far as is ætiology.

Hilversum. D. P. R. KEIZER.

PERSISTENCE OF ANTIBODIES TO RIFT VALLEY FEVER IN MAN

SIR,—The duration of the immunity in man following infection with the virus of Rift Valley fever (R.V.F.) is unknown. Sabin and Blumberg[12] found neutralising antibodies for R.V.F. virus in the serum of a patient who had been infected twelve years before and had not been exposed to the virus since. The reviews by Todd[13] and Schrire and Gear[14] give a figure of twenty years, but we have failed to find the protocols and we believe the figure is without foundation.

In 1931, Daubney brought a strain of the newly isolated R.V.F. virus to England. One of us (T. D.) inoculated the virus into two lambs which were moribund within thirty-six hours. T. D. fell ill with R.V.F. five and a half days later.[15] After recovery he had no further contact with the virus, and twenty-five years later we detected neutralising antibodies in his serum. The serum was not inactivated and was titrated against 250 LD_{50}s of R.V.F. virus in mice, using ten mice per dilution of serum. The titre of the serum, expressed as the reciprocal of the 50% neutralising dilution, was $10^{1.8}$.

East African Veterinary Research Organisation, Muguga, Kenya, and The Food and Agriculture Organisation, Rome.

R. D. BROWN
G. R. SCOTT
T. DALLING.

11. Bolk, L. *Ned. Tidjschr. Geneesk.* 1923.
12. Sabin, A. B., Blumberg, R. W. *Proc. Soc. exp. Biol., N.Y.* 1947, **64**, 385.
13. Todd, F. A. Foreign Animal Diseases. Trenton, New Jersey, 1954; p. 156.
14. Schrire, L., Gear, J. *Cent. Afr. J. Med.* 1956, **2**, 237.
15. Findlay, G. M. *Trans. R. Soc. trop. Med.* 1932, **25**, 229.

EFFECT OF ANTIBIOTICS ON PURULENT SPUTUM

SIR,—In their recent article (Aug. 3), Dr. Douglas and his colleagues say that "routine bacteriological examination of the sputum was of no value in predicting the response to treatment with any of the three antibiotics used." While this conclusion is undoubtedly true in certain circumstances, it does, we think, require further qualification.

Although Dr. Douglas and his colleagues attempted to avoid sampling errors in the cultures of individual sputum specimens by preliminary homogenisation of the sputum with pancreatin, no account was taken of the sampling errors involved in the examination of only single specimens from each patient. The authors mentioned this factor but attached little importance to it, except to point out that few routine laboratories could cope with the volume of work entailed in the examination of multiple specimens. This may be so, but proper interpretation of the cultures from *single* specimens can be made only in the light of experience of the findings from multiple ones, which cannot therefore be ignored.

In this laboratory we have on many occasions cultivated several specimens of purulent or mucopurulent sputum from individual patients with chronic bronchitis and observed that, whereas no pathogenic organism could be found in one specimen, in another there was a very heavy growth of one—usually *Hæmophilus influenzæ*. Perhaps the most striking example was that of a bronchitic who expectorated two lumps of pus within ten minutes. In culture no *H. influenzæ* could be found in one specimen but in the other this organism constituted 91% of the total colonies present. The response of this patient to chemotherapy was completely in accord with the supposition that *H. influenzæ* was the pathogen.

That variations as large as this are seen between specimens indicates that the concept of the "predominant" organism being the significant organism, especially in single specimens, is meaningless. The mere presence of an organism in a culture should be given the same significance as if it were predominant; and the absence of an organism from a single specimen has little significance (cf. tuberculosis).

In our experience the greatest variations in distribution of organisms, both within and between specimens of sputum, are found with *H. influenzæ*, and careful studies, based on multiple specimens, of the clinical and bacteriological responses of chronic bronchitics to chemotherapy have left us in no doubt of the overriding importance of this organism as a pathogen.[1–3] Our findings are in complete accord with those of Mulder et al.[4] Of the other recognised respiratory pathogens only the pneumococcus seems to be important, and this mainly in acute exacerbations. So convinced are we of the validity of these observations that the sputum of patients attending the bronchitis clinic at the Brompton Hospital is now seldom examined bacteriologically; and chemotherapy, if indicated clinically, is based on the assumption that both organisms are present. A combination of penicillin and streptomycin, which we use for exacerbations, or one of the tetracyclines or chloramphenicol will usually inhibit both.

Analysis of the effects of antibiotics on the bacterial flora in chronic bronchitis requires careful attention to the possible sources of sampling errors mentioned above. Taking these into account, the response to penicillin can be shown to be entirely in accord with the supposition that *H. influenzæ* and the pneumococcus are pathogens in purulent bronchitis.[5] The pneumococcus is so highly sensitive to penicillin that very small doses usually

1. May, J. R. *Lancet*, 1953, ii, 534.
2. May, J. R. *Ibid*, p. 899.
3. May, J. R. *Ibid*, 1954, ii, 839.
4. Mulder, J., Goslings, W. R. O., van der Plas, M. C., Lopes Cardozo, P. *Acta med. scand.* 1952, **143**, 32.
5. May, J. R. *Brit. J. Tuberc.* 1955, **49**, 166.

suppress it. *H. influenzæ*, however, is much more resistant, and is seldom suppressed by doses of less than 8 mega units daily.[6] The similar results obtained by Dr. Douglas and his co-workers with 1 mega unit and 2 mega units daily, therefore, are not unexpected, since both of these doses would normally suppress pneumococci and neither would suppress *H. influenzæ*. The high sputum levels attainable with 2 mega units of the di-ethyl-amino-ethyl ester of penicillin, however, would often suppress the latter organism.[5]

The impressive results obtained by Dr. Douglas and his colleagues with chloramphenicol are in agreement with our own, but, since in severe chronic bronchitis chemotherapy is likely to be required frequently or for long periods, we feel that the risks of blood dyscrasias are too great ever to allow its use for this purpose and we prefer to use tetracycline or oxytetracycline instead.[7]

In conclusion, therefore, we would suggest that the results obtained by Douglas et al. are, broadly speaking, in keeping with the belief that *H. influenzæ* and the pneumococcus are the important pathogens in chronic bronchitis (and, we believe, bronchiectasis, though our experience of this condition has not been so great), and we would agree that the routine bacteriological examination of sputum may well be unhelpful unless strict attention is paid to *all* possible sampling errors.

Institute of Diseases of the Chest, Brompton, London, S.W.3. J. ROBERT MAY
NEVILLE C. OSWALD.

SIR,—The interesting article by Dr. Douglas and his colleagues prompts the question of a control series. One recalls that many patients with exacerbations of purulent bronchitis had spontaneous remissions in one or two weeks, without the use of antibiotics. It would be of interest to know if the investigation showed how much these spontaneous remissions were shortened by antibiotic treatment.

Danby, near Whitby, Yorkshire. R. A. ROBINSON.

TREATMENT OF HEPATIC COMA

SIR,—Last week's annotation recommended enemas and purges with a broad-spectrum antibiotic to prevent further intoxication from intestinal bacteria.

Choosing a laxative which can be prescribed safely with antibiotics which are themselves liable to disturb the bowel by changing its flora, presents a problem on more occasions than this—for instance, before abdominal surgery. A peculiar property of senna might be turned to account. In its pure form (e.g., 'Senokot') the active principles, which pass through the blood-stream,[8] are released from the senna glycosides only so long as coliform bacilli are present to provide the necessary enzymes,[9] and therefore purgation should be limited by the antibiotic exerting its full effect.

Bacteriology Department, University of Glasgow. J. E. TINNE.

TREATMENT OF MIGRAINE

SIR,—Dr. Leyton (Aug. 3) is convinced that migraine (periodic headache) "is a definite organic complaint . . ." This statement is contrary to research.[10 11] Migraine seems to be a psychosomatic reaction and should be treated as such.[12 13] The fact that 'Serpasil' dramatically relieved two of his patients suggests that its sedative effect abolished the anxiety and tension that go hand in hand with this symptom.[14]

I humbly suggest that if Dr. Leyton would work with a physician versed in psychological medicine, he would get even better results in his clinic.

London, W.1. GORDON AMBROSE.

PULLING THE UMBILICAL CORD

SIR,—I once observed the birth of kittens to a Siamese cat.

At long intervals, without sign of maternal distress, they slid out like large drops of kitten rather than solid objects. They were a mixed bag, coloured blue-grey, black, and blotched black and white. *Apartheid* had not been much in her thoughts during the mating period. Soon she began to take special interest in one kitten that was not stirring at all. She seized the severed cord in her teeth and gave it some vigorous tugs. The kitten made no response. She did the same to another without result. Afterwards I found that these kittens were dead.

Evidently the mother's instinct was to pull on the cord to start respiration. Is this instinct rational in any way, either in cats or humans?

Bewdley, Worcestershire. G. S. LAWRENCE.

PENICILLIN TREATMENT OF LEPTOSPIROSIS

SIR,—84 consecutive patients with laboratory-proved leptospirosis among security forces in Malaya have been treated with intramuscular penicillin in this hospital. 600,000 units of crystalline penicillin were administered intramuscularly as soon as a provisional diagnosis of leptospirosis was made, and repeated four-hourly for twenty-four hours and then six-hourly to complete seven days.

The accompanying table shows on what day of the disease penicillin therapy was started, and its effect on the duration of the fever.

TIMING AND EFFECT OF PENICILLIN TREATMENT

Day of disease when penicillin first given	No. of cases	Duration of pyrexia after start of treatment (hr.)	
		Range	Average
2nd	4	12–30	20
3rd	15	8–30	16
4th	25	5–30	17
5th	26	10–30	18
6th +	14	14–60	34

Within four to six hours of the first injection 70 patients (83% of all cases and 89% of those treated within five days of the onset of the illness) had what was tantamount to a Jarisch-Herxheimer reaction. 59 (84%) had a sharp rise in temperature, and 58 (83%) a severe fall in blood-pressure. In addition, in 31 cases (44%) there was a precipitation or aggravation of classical symptoms and signs of leptospirosis. All 70 (83% of all cases) treated within five days of the estimated date of onset of the illness shared in this elevation of pyrexia and fall of blood-pressure in some measure. The reaction was mild to moderately severe in 60 (86% of affected cases) and severe in 10 (14%).

The nurses became quite alarmed with this reaction to penicillin, during which the patients appeared collapsed and desperately ill. We gave no stimulants but continued treatment, and within twenty-four hours the patients were completely recovered from their reaction. The duration of the reaction roughly equalled the duration of pyrexia following the start of penicillin therapy.

This type of reaction has been noted elsewhere during penicillin therapy of leptospirosis. We came to regard it as a sign of good response to treatment and as a diagnostic sign. It is now known in this hospital as the diagnostic penicillin-leptospiral response.

In some cases where the blood culture was positive, the agglutination titre in the second specimen normally taken by us after the fifteenth day of disease was far from being diagnostic of leptospirosis. This is believed to be due to an unusually slow production of antibodies—the result of early and adequate penicillin therapy.

6. Goslings, W. R. O., Hers, J. F. P. *Acta med. scand.* 1953, **146**, 127.
7. May, J. R., Oswald, N. C. *Lancet*, 1956, ii, 814.
8. *Ibid*, 1952, i, 655.
9. Abrahams, A. *In* British Encyclopædia of Medical Practice interim supplement, 1954, **138**, 3.
10. Fromm-Reichman, F. *Psychoanalyt. Rev.* 1937, **24**, 26.
11. Eisenbud, J. *Psychiat. Quart.* 1937, **11**, 592.
12. Weber, H. *Brit. J. Psychol.* 1932, **12**, 151.
13. Wolff, H. G. *Arch. Neurol. Psychiat.* 1937, **37**, 895.
14. Ambrose, G., Newbold, G. Handbook of Medical Hypnosis. London, 1956; p. 75.

There were no deaths and no relapses; in no case did polyuria or a low specific-gravity urine develop.

Our results leave no doubt in our minds about the efficacy of penicillin therapy in leptospirosis, begun within the first five days of the illness; and we have reason to believe that the absence of relapses and the maintenance of the concentrating power of the kidney (even in the post-anuric phase) suggests the beneficial effect of penicillin in cases first treated after the fifth day of the illness.

This work is the subject of a paper which will be published in the *Journal of the Royal Army Medical Corps*.

British Military Hospital, Kinrara, Kuala Lumpur, Malaya.

JOHN MACKAY-DICK
J. F. ROBINSON.

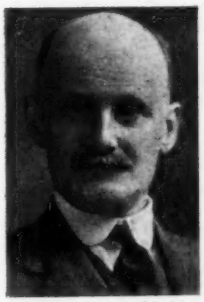
Obituary

ANDREW FERGUS HEWAT

M.D. Edin., F.R.C.P.E., F.R.F.P.S., F.R.S.E.

Dr. A. Fergus Hewat, consulting physician to the Royal Infirmary, Edinburgh, and a past president of the Royal College of Physicians of Edinburgh, died on Aug. 3.

Fergus Hewat was born in Edinburgh in 1884, the son of Archibald Hewat, vice-president of the Faculty of Actuaries. He received his early education at Edinburgh Academy before entering the university, where he qualified M.B. in 1907. Among his early honours was the presidency of the Royal Medical Society. In the following years he widened his experience by means of diverse junior appointments at the Royal Infirmary and other hospitals. His early intention was to be a pædiatrician; but in 1915 his career was interrupted by service in the R.A.M.C., which quickened his interest in diseases of the chest. After returning to Edinburgh he was appointed assistant to the professor of tuberculosis, Sir Robert Philip; and Philip and Prof. Edwin Bramwell, whom he joined a few years later as assistant physician to the Royal Infirmary, strongly influenced him in his subsequent career.



[*A. Ayton*

In 1925 Dr. Hewat was awarded a gold medal for his thesis—a painstaking study of the anatomy of lung and pleura, which formed the basis of a Honyman Gillespie lecture in 1937. In 1936, on Bramwell's retirement, he became full physician to the Royal Infirmary. He was president of the Royal College of Physicians in 1943–45, having previously served the college as secretary (1932–36) and as curator of the laboratory. In the years after the late war, when he had retired from his hospital appointments, he remained medical adviser to a large life assurance company, and only three years ago he wrote jointly an important paper on medical aspects of life-assurance underwriting (see *Lancet*, 1954, ii, 1168).

W. R. R. writes:

Dr. Fergus Hewat will be remembered well by some thousands of Edinburgh graduates. He belonged to a type of physician and clinical teacher who is disappearing. Like many other distinguished men of his generation he would probably have failed to pass the entrance examinations which are now required of those who wish to study medicine; but if he lacked the academic ability of some of his contemporaries, he more than made up for this by the scrupulous and conscientious way in which he gave of his best to both students and patients. He treated his students as equals, with every understanding for their inadequacies. Sarcastic remarks were never used; but he was often critical of others, for he expected a high sense of duty and propriety from his colleagues. At times he felt suspicious of young professors with new ideas, who seemed to him to belittle the hard spade-work needed to maintain the clinical teaching traditions of Edinburgh Royal Infirmary. On the other hand he never tired of referring to his admiration for Sir Robert Philip and Prof. Edwin Bramwell, with each of whom he had been closely associated for many years.

As a close colleague he was loyal, unselfish, and helpful, while general practitioners knew they could count absolutely on his support and advice in difficult situations. As a physician he inspired confidence by his skill, frankness, and kindly interest in the patient's personal problems. He was popular as a bedside teacher and took endless trouble to prepare his lectures. Though he added little of note to existing knowledge, the influence he exerted on medical students was great, and was all for the good. Diagnosis, side-room tests, medical ethics, problems of life assurance, details of management, drug treatment, and speaking to relatives were also considered in a highly practical and forceful manner which probably influenced us all much more than we now realise. Scientific medicine seems now to discourage this type of teacher, and yet who can measure the influence of an enthusiastic and devoted teacher of Fergus Hewat's type on the young student? As a friend and counsellor, Fergus will be missed by many.

A former house-physician writes:

To the youngsters around him Fergus offered friendship in generous measure, and they responded by holding him in affectionate esteem. Seen through his eyes, his unit contained only swans; and it is heart-warming, even after twenty years, to recall his intemperate inflation of a junior's halting efforts. The prentice paper? It was going to set the *Q.J.M.* ablaze. And that drab M.D. thesis? A gold medal, my boy, nothing less. The geese were elsewhere; and sometimes he was enraged with them. But it was an ephemeral rage, with no lingering rancour; and if a brave one chided him on his hastiness he would pause, glare, and then smile in silent confession of his foible. His likeability did not account alone for the popularity of his clinic or for the respect that he commanded: he was an astute clinician and a man of solid convictions from whom we learnt much of how to diagnose cases and treat patients, and to comport ourselves. He was a better teacher than he thought.

Dr. Hewat is survived by his widow.

Appointments

BATTEN, J. C., M.D. Lond., M.R.C.P.: part-time consultant in general medicine, St. George's Hospital group.

FAIRBURN, E. A., M.D. Lond., M.R.C.P.: part-time consultant physician, skin department, United Birmingham Hospitals.

MCGRATH, P. G., M.B. Glasg., D.PSYCH.: medical superintendent, Broadmoor Institution, Crowthorne, Berkshire.

REES, L. T., M.B. Wales, F.F.A. R.C.S., D.A.: consultant anæsthetist based at Royal Gwent Hospital, Newport, Monmouthshire.

YOUNG, S. M., L.R.C.P.E., D.P.H.: depute M.O.H. and depute port M.O., Greenock.

East Anglian Regional Hospital Board:

ASHFORD, G. L., M.B. Edin., D.P.M.: consultant psychiatrist and deputy medical superintendent, Little Plumstead Hospital, Norwich.

LISTER, I. S., M.B. Camb.: surgical registrar, United Norwich Hospitals.

SHRIVASTAVA, B. D., M.B. Agra, D.O.: ophthalmic registrar, Norfolk and Norwich Hospital.

Manchester Regional Hospital Board:

ASHWORTH, ARNOLD, M.B. Manc., F.R.C.S.: part-time consultant urologist, Manchester, Salford, South Manchester, Booth Hall, and Monsall Hospitals.

DUNN, J. F., M.B. Glasg., D.P.M.: assistant psychiatrist, Lancaster Moor Hospital.

HERAPATH, J. C., M.D. Wales, M.R.C.P.: part-time consultant geriatrician, Blackpool and Fylde group of hospitals.

South-Western Regional Hospital Board:

BLOTT, KATHLEEN, M.B. Brist., F.F.A. R.C.S., D.A.: consultant anæsthetist, Bristol clinical area.

BROWNE, JAMES, M.D. Belf., D.P.M.: consultant psychiatrist, St. Lawrence's Hospital, Bodmin.

COUPER, LEWIS, M.B. Glasg., D.P.M.: consultant psychiatrist and medical superintendent, Digby-Wonford Hospital, Exeter.

Lancashire County Council:

DYER, J. V., M.B. Lond., D.P.H.: assistant divisional M.O.

HAIGH, KATHLEEN, M. C., M.B. Leeds, D.OBST.: assistant divisional M.O.

HARRIS, CHARLES, M.B. Dubl.: assistant divisional M.O.

HOLT, P. G., M.B. Lpool, D.P.H.: assistant divisional M.O.

SIPPERT, ALAN, M.B. Manc.: assistant divisional M.O.

TIMPANY, MARGARET M., M.B. Edin., D.P.H.: assistant divisional M.O.

Births, Marriages, and Deaths

BIRTHS

BREWERTON.—On August 7, at the South London Hospital, to Joan (formerly Wells) and Derrick Brewerton—a son.

Notes and News

AN OLD TRANQUILLISER

Sir Compton Mackenzie's history of tobacco [1] is a most dangerous and perhaps an immoral book. It describes and even seems to approve a dirty habit which has been shown (statistically) to cause cancer of the bronchus and, if several recent papers are credible, some other unpleasant diseases of our later years. It tells the tale of Raleigh the high-flyer and snuffling scratching James from Scotland; of Cavendish and Negrohead; of the Oriental Divan in Regent Street, and of the war between the Imperial Tobacco Company and their American rivals. The stories have never been told better, but richer by far are the reminiscences of a hardened and unrepentant addict. To those who have sat in the warmth of Sir Compton Mackenzie's casual conversation one chapter of such personal history is not enough, but for posterity it will be a mine as rich as *The Table Talk of Samuel Rogers*. Smoking is today less popular with the young than with the old (though the Minister of Health has less to do with this than the Chancellor of the Exchequer). Soon it is likely to be unfashionable, then evidence of ill-breeding, and finally downright indecent. When this most blessed vice is finally under the ban of presbyter and/or commissar the fortunate owner of this book—concealed behind the volumes of Origen and Marx—will find it a wonderful comfort against the oppressions of this world.

PREVENTION OF BYSSINOSIS

CHEST disorders are common among card-room workers in the cotton industry. This high prevalence is accounted for partly by a high rate of chronic bronchitis and other chest diseases in areas where they live, and partly by byssinosis due to dust in the card-rooms. A new report [2] recommends the Shirley pressure-point system of exhaust ventilation in card-rooms. The three cylinders of the carding-engine act as a fan, creating zones of high and low air-pressure. The Shirley system is designed to relieve the high-pressure zones and remove the dust which would otherwise be liberated from them into the atmosphere. The device has been exhaustively tested at the Shirley Institute and in a full-scale installation in a mill. In a foreword Sir George Barnett, the Chief Inspector of Factories, commends this system as a means of preventing byssinosis.

RETURN OF THE DOCTOR

BORN and educated in South Africa, the pseudonymous Dr. Vane [3] came to England to study medicine at Cambridge and St. Thomas's Hospital. After ten years' absence he returned to Africa, and he has now described his experiences as medical officer to a gold-mining company in the Transvaal and of surgery among Negroes in the Belgian Congo, Sierra Leone, and the Gold Coast. Dr. Vane evidently knows and loves his Africans, and is blind neither to their faults nor their attractive qualities. He gives interesting accounts of the methods of native witch-doctors, some of whom seem to be westernised in both dress and financial acumen, and of a trip which he and his wife made, partly by tandem, to the pygmies near Lake Kivu in the Congo.

ACCESS TO RUSSIAN JOURNALS

FOR the past ten years the Excerpta Medica Foundation through its abstracts of medical literature has opened to medical readers many journals which would otherwise have been closed to them by reason of distance, shortage of time, or an unfamiliar language. The abstracts offer almost comprehensive cover, and it was all the more unfortunate that their sole considerable gap should have been one that it is impossible for the ordinary reader to fill from his own resources: doctors in all branches of medicine will welcome the news that *Abstracts of Soviet Medicine* has begun to appear. This will be published quarterly, in two parts. Part A will cover the basic medical sciences, and part B clinical medicine. The first issue of part A has been selected and prepared by the foundation's Russian editorial contributors, who have been appointed by the Academy of Medical Sciences of the U.S.S.R. The annual subscription to each part will be £5 13*s*. (combined subscription £9 10*s*.). Further particulars may be had from the foundation, 111, Kalverstraat, Amsterdam, Holland.

1. Sublime Tobacco. By COMPTON MACKENZIE. London: Chatto & Windus. 1957. Pp. 352. 21*s*.
2. Dust In Card Rooms: Third Interim Report of the Joint Advisory Committee of the Cotton Industry. H.M. Stationery Office. 1957. Pp. 30. 2*s*. 6*d*.
3. Black Magic and White Medicine. By MICHAEL VANE. Edinburgh: W. & R. Chambers. 1957. Pp. 254. 16*s*.

University of London

The title of reader in anatomy has been conferred on Dr. T. W. Glenister in respect of his post at Charing Cross Hospital Medical School.

University College of North Wales

Mr. Charles Evans, F.R.C.S., deputy leader of the British expedition which climbed Mount Everest, has been appointed principal of the college.

Chartered Society of Physiotherapy

The annual congress of this society will be held at St. Pancras Town Hall, London, N.W.1, from Sept. 19 to 21. In the opening lecture Prof. C. G. Rob will speak on arterial surgery, and Prof. W. R. Spurrell will deliver the founders' lecture. Doctors are invited to attend the meetings, and full programmes and tickets of admission may be had from the secretary of the society, Tavistock House (South), Tavistock Square, W.C.1.

National Health Service Tribunal

Since this tribunal was appointed there have been several changes in the membership of the tribunal and the panels. The chairman is Sir Reginald Taaffe Sharpe, Q.C., and the member appointed by the Minister after consultation with associations representing executive councils is Mr. Henry Lesser. The panel from which the practitioner members are selected is: Dr. H. Guy Dain, Dr. A. J. R. Hudson, Dr. C. F. R. Killick, Dr. A. Talbot Rogers, Dr. F. M. Rose, and Dr. A. S. Wilson. The panel of ophthalmic medical practitioners is: Mr. J. S. Arkle, Mrs. Dorothy Campbell, Dr. R. R. Garden, Mr. R. Affleck Greeves, Dr. T. G. W. Parry, and Mr. A. M. Reid.

British Medical Association Prizes

The British Medical Association offers the following prizes and scholarships:

The Sir Charles Hastings clinical prize (£75) and the Charles Oliver Hawthorne clinical prize (£50) are awarded, to members of the association who are in general practice, for unpublished work based on personal experiences, submitted by Dec. 31, 1957.

A prize of about £25 is offered to medical students for an essay on the Value of Observation in the Training of Medical Students. One or more prizes of £50 are offered to provisionally registered practitioners for an unpublished essay on What I have Learned from Contact with the Patient's Relatives. These essays must be submitted by Jan. 31, 1958.

The Ernest Hart scholarship (£300), Walter Dixon scholarship (£300), and four ordinary research scholarships (£200) are offered for medical research. The scholars need not be engaged full-time. Applications must be submitted by March 1, 1958.

Details may be had from the secretary of the association, B.M.A. House, Tavistock Square, London, W.C.1.

Training of the District Nurse

The Minister of Health has broadly accepted the majority recommendations of the working party on the training of district nurses (see *Lancet*, 1955, ii, 543). One of these was that a committee should be appointed whose duties would include the setting of examinations. The Minister has decided, however, that the committee shall be advisory only. His nominees are Mr. D. H. Ingall, D.SC., the chairman, and Miss E. Jackson. The other ten members were nominated by other organisations: Miss V. M. King, Dr. A. Elliott, and Mr. C. W. Read, PH.D., by the County Councils Association; Miss I. H. Morris, Prof. A. B. Semple, M.D., and Mr. F. L. Freeman by the Association of Municipal Corporations; Dr. E. F. Egan by the London County Council; Dr. Mary Esslemont by the British Medical Association; Miss Dora Williams by the Queen's Institute of District Nursing; and Miss E. M. Wearn by the Royal College of Nursing. The committee will advise the Minister on schemes of training and examinations submitted by local health authorities.

Copies of the first four issues of THE LANCET for 1949 (Jan. 1, Jan. 8, Jan. 15, and Jan. 22) are needed to complete a set for the Central Medical Library in Moscow. We should be grateful if any reader would care to supply the missing copies.

Dr. David Harley is to speak at the joint congress of the West German Allergy and Ophthalmological Societies to be held in Heidelberg in September.

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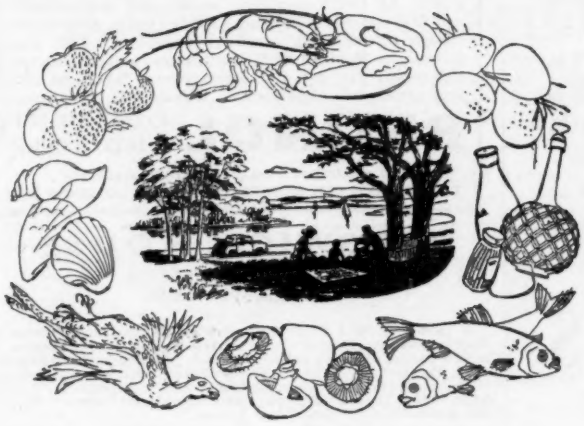

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The Terms and Conditions of Service of Hospital Medical and Dental Staff apply to all N.H.S. hospital posts we advertise, unless otherwise stated. Canvassing disqualifies, but candidates may normally visit the hospital by appointment.

Academic and Educational

EXAMINING BOARD IN ENGLAND

by the
ROYAL COLLEGE OF PHYSICIANS OF LONDON
and the
ROYAL COLLEGE OF SURGEONS OF ENGLAND

Notice is hereby given that the following EXAMINATIONS will commence on the dates stated below :

DIPLOMA IN CHILD HEALTH
18th September
DIPLOMA IN MEDICAL RADIOTHERAPY
10th October
DIPLOMA IN MEDICAL RADIO-DIAGNOSIS
Part II—24th October
DIPLOMA IN PATHOLOGY
31st October

Applications and fees for either or both Parts of an Examination must reach the Secretary, Examination Hall, Queen-square, London, W.C.1, at least 21 days before Part I of the Examination begins. FRANCIS M. STENT, Secretary.

COURSE IN ORTHOPÆDIC SURGERY

HARLOW WOOD ORTHOPÆDIC HOSPITAL, near MANSFIELD, NOTTS

21ST OCTOBER–25TH OCTOBER, 1957

21st Oct.	Introduction	
	The Rehabilitation of the Orthopædic Patient	Mr. S. A. S. MALKIN with Mr. J. D. MALLOCH
	Fractures of the Spine	Mr. E. A. NICOLL
22nd Oct.	The Sequelæ of Polio-myelitis	Mr. W. J. SHARRARD
	Diagnosis and Treatment of Spinal Lesions in Orthopædic Practice	Mr. A. N. BIRKETT
	Hand Surgery	Mr. R. G. PULVERTAFT with Mr. D. A. REID
23rd Oct.	Hand Surgery	Mr. R. G. PULVERTAFT
	Osteoarthritis of the Hip	Mr. J. P. CAMPBELL
24th Oct.	Orthopædic Tuberculosis	Mr. J. P. JACKSON
	The Surgical Management of Rheumatoid Arthritis	Mr. L. MORRIS
	Avascular necrosis of bone	Mr. H. JACKSON-BURROWS
	Paralytic Dislocation of the Hip	Mr. W. WAUGH
25th Oct.	Low Spinal Fusion	Mr. E. W. O. ADKINS
	Treatment of Paraplegia	Mr. F. W. HOLDSWORTH
	Spondylolisthesis	Dr. J. BARR (Boston—Mass.)

No fee for the course.

Applications to be sent to Secretary, Harlow Wood Orthopædic Hospital. Limited accommodation available, if required, at associated Hospital.

ANÆSTHETICS COURSE

A 2 WEEKS COURSE OF LECTURES, DEMONSTRATIONS AND TUTORIALS for postgraduates preparing for higher Diplomas in Anæsthetics will be held from 14TH to 25TH OCTOBER, 1957.

Fees : Lectures and Demonstrations £15 15s.
Tutorial Discussion Groups £10 10s.

Further details and application forms may be obtained from Mr. W. F. DAVIS, Secretary, Faculty of Anæsthetists, Royal College of Surgeons of England, Lincoln's Inn-fields, London, W.C.2 (Tel. HOLborn 3474).

THE UNIVERSITY OF LIVERPOOL. Applications are invited for 2 posts as ASSISTANT LECTURER or LECTURER in the Department of Pathology. The salary range for an Assistant Lecturer will be £900–£1100 p.a. ; the initial salary for a Lecturer will be within the range £1200–£1500 p.a., according to qualifications and experience.

Applications, stating age, academic qualifications and experience, together with the names of 3 referees, should be received not later than 31st August, 1957, by the Registrar, from whom further particulars of the conditions of appointment may be obtained.

THE UNIVERSITY OF MANCHESTER. Applications are invited for the full-time post of LECTURER IN CLINICAL PATHOLOGY from suitably qualified graduates in medicine. Candidates should have wide experience in clinical pathology, and special interests in bacteriology. High qualifications in these subjects are desirable, and there are ample facilities available for research. Salary on a scale rising to £2150 p.a. ; initial salary according to qualifications and experience. Duties to commence as soon as possible. Membership of F.S.S.U. and children's allowance scheme.

Applications should be sent not later than 31st August, 1957, to the Registrar, the University, Manchester, 13, from whom further particulars and forms of application may be obtained.

UNIVERSITY OF OXFORD, RADCLIFFE INFIRMARY, DEPARTMENT OF PATHOLOGY. Applications are invited for the post of GRADUATE ASSISTANT in the Department. The successful applicant will take part in the teaching and diagnostic work of the Department ; there will be opportunities for original work. The commencing salary will be within a range from £700 to £1400 (the salary will be increased when the supplementation of academic salaries takes place shortly) according to qualifications and experience, with family allowance and F.S.S.U. Duties to commence in October, 1957.

Applications, together with names of 3 referees, should be sent not later than 2nd September, 1957, to Dr. A. H. T. ROBB-SMITH, Radcliffe Infirmary, from whom further particulars may be obtained.

ST. MARY'S HOSPITAL MEDICAL SCHOOL (UNIVERSITY OF LONDON), Paddington, W.2. Applications are invited for the post of Full-time ASSISTANT DIRECTOR of the Surgical Unit for an initial period of 3 years. Salary within the scale £1800–£100–£2500, together with superannuation under the F.S.S.U. and children's allowance.

Applications (2 copies), with names of 3 referees, should be submitted by 7th September to the Secretary, from whom further particulars may be obtained.

Hospital Services : Senior Appointments

NORTH WEST METROPOLITAN REGIONAL HOSPITAL BOARD.

(1) CONSULTANT ORTHOPÆDIC SURGEON (3 half-days a week), Harefield and Northwood Group of hospitals. Duties mainly concerned with trauma at Mount Vernon Hospital Northwood, Middlesex (551 Beds), which may be visited by direct appointment.

Applications before 16th September, 1957.

(2) CONSULTANT RADIOLOGIST (5 half-days a week) ; 3 half-days to be spent at Finchley Memorial Hospital, Granville-road, N.12 (76 Beds), and 2 half-days at Friern Hospital, New Southgate, N.11 (2470 Beds). Hospitals may be visited by direct appointment.

Applications before 19th September, 1957.

Application forms obtainable from, and returnable to, Secretary, North West Metropolitan Regional Hospital Board, 11A, Portland-place, W.1.

ROYAL MARSDEN HOSPITAL, Fulham-road, S.W.3. Applications are invited for the full-time appointment of ASSISTANT RADIOTHERAPIST (Senior Hospital Medical Officer grade). Salary £1653 15s. at age 32. Candidates must hold a Diploma in Medical Radiology.

Applications (12 copies), quoting age, education, qualifications and experience and giving the names of 3 referees, should be sent to the House Governor by 30th August, 1957.

SOUTH WEST METROPOLITAN REGIONAL HOSPITAL BOARD requires Whole-time CONSULTANT RADIOLOGIST for the Wandsworth Group. Duties mainly at St. James' Hospital, Balham, S.W.12. Candidates must have D.M.R. and wide experience in radiology.

Applications by letter (5 copies), giving date of birth, qualifications, experience, and names of 3 referees, to Secretary (S.1), South West Metropolitan Regional Hospital Board, 11A, Portland-place, W.1, by 14th September, 1957. Applicants may visit hospitals by local arrangement.

SOUTH WEST METROPOLITAN REGIONAL HOSPITAL BOARD requires Part-time CONSULTANT ANÆSTHETIST (6 half-days per week) for the Lambeth Group of hospitals. 4 of the sessions are for ophthalmic work and 2 for general work.

Applications by letter (5 copies), giving date of birth, qualifications, experience, and names of 3 referees, to the Secretary (S.1), South West Metropolitan Regional Hospital Board, 11A, Portland-place, W.1, by 14th September, 1957. Applicants may visit hospitals by local arrangement.

SOUTH WEST METROPOLITAN REGIONAL HOSPITAL BOARD requires Part-time ASSISTANT OPHTHALMOLOGIST (Senior Hospital Medical Officer grade) (1 half-day per week) in the Wandsworth Group. Duties at the Ophthalmic Outpatient Clinic at St. James' Hospital, Balham, on Thursday afternoons.

Applications (5 copies), giving date of birth, qualifications, experience, and names of 3 referees, to Secretary (S.1), South West Metropolitan Regional Hospital Board, 11A, Portland-place, W.1, by 14th September, 1957. Applicants may visit Hospital by local arrangement.

THE HOSPITAL FOR SICK CHILDREN, Great Ormond-street, London, W.C.1. There will be a vacancy in October, 1957, for a Part-time MEDICAL OFFICER to the Cardio-thoracic Unit (4 sessions per week).

Further particulars and form of application, which must be returned not later than 9th September, 1957, are obtainable from the undersigned.

H. F. RUTHERFORD, House Governor and Secretary.

CROWTHORNE, BERKSHIRE. BROADMOOR INSTITUTION. (920 Beds for persons of unsound mind of criminal tendencies.) Whole-time CONSULTANT. Wide experience in psychiatry, and the D.P.M. necessary. Duties may involve attendance at outpatient clinics. House available.

Applications, naming 3 referees, to Medical Superintendent by 7th September, 1957. Candidates may visit Institution by appointment.

LEEDS REGIONAL HOSPITAL BOARD. Applications are invited from medical practitioners for the appointment of ASSISTANT SENIOR MEDICAL OFFICER on the staff of the Senior Administrative Medical Officer at the Board Headquarters, Harrogate, at a salary of £1680–£80(4)–£100(1)–£2100 p.a. The officer concerned will be required to assist generally the Senior Administrative Medical Officer and particularly with the administration of the Board's Mental Health Services, for which expert psychiatric advice will be available. Previous experience of medical administration and a knowledge of mental health work, although not essential, would be considered an advantage.

Applications, with full details of qualifications and experience, together with the names of 3 referees, to be sent to the Secretary, Park-parade, Harrogate, by 14th September, 1957.

LEEDS REGIONAL HOSPITAL BOARD. Locum Tenens CONSULTANT or SENIOR HOSPITAL MEDICAL OFFICER in Ophthalmology (8 notional half-days per week), Scarborough and Bridlington. Vacant now—month to month basis.

Applications, stating age, qualifications and details of appointments held showing dates, together with the names and addresses of 3 referees, to the Secretary, Park-parade, Harrogate, as soon as possible.

LEEDS REGIONAL HOSPITAL BOARD. Applications are invited from medical practitioners for the appointment of REGIONAL PSYCHIATRIST. The person appointed will be employed for 7/11ths of his time on administrative duties on the staff of the Senior Administrative Medical Officer at the Board's Headquarters, Harrogate (salary scale, whole-time £2300–£2875 p.a.), and for 4/11ths of his time on Consultant clinical work (salary scale, whole-time £2205–£3255 p.a.). The proportion of time spent on administrative and clinical duties will be subject to review from time to time. It is hoped that arrangements will be made for the successful candidate to work in association with the Leeds University Department of Psychiatry for at least 1 session per week. Candidates should hold high qualifications in medicine and psychiatry and have wide experience in general psychiatry, including administrative experience of both inpatient and outpatient work.

Applications (12 copies), with full details of qualifications and experience together with the names of 3 referees, to be sent to the Secretary, Park-parade, Harrogate, by 14th September, 1957.

MANCHESTER REGIONAL HOSPITAL BOARD. Whole-time or maximum Part-time CONSULTANT RADIOTHERAPIST, Christie Hospital and Holt Radium Institute, Manchester. F.F.R. essential, other higher medical or surgical qualifications desirable.

Application forms from the Senior Administrative Medical Officer to the Board, Cheetwood-road, Manchester, 8, to be returned by 2nd September, 1957.

MANCHESTER REGIONAL HOSPITAL BOARD. Applications are invited for the post of Locum CONSULTANT SURGEON (8 notional half-days per week) with the Stockport and Buxton Hospital Management Committee. The main duties will be at Stockport Infirmary and Stepping Hill Hospital. Salary according to individual status.

Applications, stating age, qualifications and details of appointments held, together with the names of 2 referees, to the Secretary, Stockport and Buxton Hospital Management Committee, 59B, Shaw-heath, Stockport.

MANCHESTER (near). PRESTWICH HOSPITAL. SENIOR HOSPITAL MEDICAL OFFICER (Locum Tenens) required at above Hospital. Must have considerable experience in psychiatric practice and hold D.P.M. Single quarters available, or may be non-resident.

Applications, giving full details of experience and names and addresses of 2 referees, should be sent immediately to Medical Superintendent, Prestwich Hospital, Prestwich, near Manchester.

NEWCASTLE REGIONAL HOSPITAL BOARD. Senior CASUALTY OFFICER (whole-time), Hartlepools Group of hospitals—main hospitals: General (466 Beds); Hartlepools (112 Beds); Cameron (73 Beds). Population served 130,891. The appointee will be required, subject to the supervision of the Senior General Surgeon and Senior Orthopædic Surgeon, to organise the casualty work throughout the Hospital Group, the main centre being at Hartlepools Hospital. Salary within range of £1653 15s.–£2126 5s. or £1548 15s.–£2126 5s. according to age. Duration of tenure of appointment not exceeding 4 years. Married accommodation available.

Applications, with names and addresses of 3 referees, to Senior Administrative Medical Officer, Regional Hospital Board, Benfield-road, Newcastle upon Tyne, 6, within 28 days.

NORTH EAST METROPOLITAN REGIONAL HOSPITAL BOARD.

Full-time CONSULTANT PSYCHIATRIST to Runwell Hospital, near Wickford, Essex, with clinics in Southend-on-Sea Group of hospitals. House available on estate.

Part-time ASSISTANT PSYCHIATRIST (Senior Hospital Medical Officer grade) at mid-Essex Child Guidance Clinic, 146, Broomfield-road, Chelmsford, for 5 sessions a week.

Applications (6 copies), stating post concerned, and names of 3 referees, should reach the Secretary, 11A, Portland-place, London, W.1, by Saturday, 14th September.

OXFORD REGIONAL HOSPITAL BOARD. Locum RADIOLOGIST (Senior Registrar or Consultant), required now until 17th September, High Wycombe area.

Applications, stating qualifications, experience, and names of 2 referees, to Secretary, 43, Banbury-road, Oxford.

RETFORD, NOTTINGHAMSHIRE. RAMPTON HOSPITAL. (1143 Beds for mental defectives of both sexes exhibiting conduct disorders.) Whole-time DEPUTY MEDICAL SUPERINTENDENT (Consultant). Excellent opportunities for study, treatment, and training of behaviour disorders of all kinds and degrees. Wide experience in psychiatry, and the D.P.M., necessary. Post is clinical but experience in hospital administration an advantage. Duties may involve attendance at outpatient clinics. House available. Candidates may visit Hospital by appointment.

Applications, naming 3 referees, to Medical Superintendent by 7th September, 1957.

SCOTLAND. WESTERN REGIONAL HOSPITAL BOARD. Locum ASSISTANT ANÆSTHETIST required for a period of 4–6 weeks from 5th September, 1957, at the Vale of Leven Hospital, Alexandria, Dunbartonshire. Senior Hospital Medical Officer grading, or according to experience.

Applications, naming 3 referees, to the Secretary, Western Regional Hospital Board, 64, West Regent-street, Glasgow, C.2.

SCOTLAND. WESTERN REGIONAL HOSPITAL BOARD. Applications are invited for the appointment of Whole-time ASSISTANT RADIOLOGIST based at the Dumfries and Galloway Royal Infirmary. Salary (at age 32 and over) on the scale £1653 15s.–£52 10s.–£2126 5s.

Applications (16 copies), stating date of birth, qualifications, experience, present appointment, and the names of 3 referees, to reach the Secretary, Western Regional Hospital Board, 64, West Regent-street, Glasgow, C.2, not later than 30 days after the publication of this advertisement.

SCOTLAND. SOUTH-EASTERN REGIONAL HOSPITAL BOARD. Applications are invited for 2 appointments of OBSTETRICIAN AND GYNÆCOLOGIST (Consultant status) for 8 sessions, with duties respectively at the following hospitals.

(*a*) Royal Infirmary, Simpson Memorial Maternity Pavilion, and Eastern General Hospital, Edinburgh.

(*b*) Royal Infirmary, Simpson Memorial Maternity Pavilion, Chalmers Hospital Annexe, Western General Hospital, Edinburgh, and Hospitals in Hawick.

The persons appointed will be expected to take part in undergraduate and postgraduate teaching.

Apply, giving particulars of age, qualifications and previous experience, and the names of 3 referees, to the Secretary, 11, Drumsheugh-gardens, Edinburgh, 3, within 30 days.

SHEFFIELD REGIONAL HOSPITAL BOARD. Leicester ISOLATION HOSPITAL AND CHEST UNIT. Whole-time CONSULTANT PHYSICIAN with special experience in chest and heart diseases required.

Application forms and further details from Senior Administrative Medical Officer, Sheffield Regional Hospital Board, Old Fulwood-road, Sheffield, 10. Forms to be returned by 7th September, 1957.

SHEFFIELD REGIONAL HOSPITAL BOARD. CONSULTANT ORTHOPÆDIC SURGEON (maximum part-time) required. Duties, mainly at Nottingham General Hospital, include responsibility for the conduct of the Casualty Department.

Application forms and further details from Senior Administrative Medical Officer, Sheffield Regional Hospital Board, Old Fulwood-road, Sheffield, 10. Forms to be returned by 14th September, 1957.

SOUTH WEST METROPOLITAN REGIONAL HOSPITAL BOARD requires Part-time CONSULTANT ANÆSTHETIST (8 half-days per week) at Queen Mary's Hospital for Children, Carshalton, Surrey. Candidates should have had special experience in infant and neonatal anæsthesia and should be prepared to be available for emergencies.

Applications by letter (5 copies), giving date of birth, qualifications, experience, and names of 3 referees, to Secretary (S.1), South West Metropolitan Regional Hospital Board, 11A, Portland-place, W.1, by 14th September, 1957. Applicants may visit Hospital by local arrangement.

SOUTH WEST METROPOLITAN REGIONAL HOSPITAL BOARD require a Locum Tenens PÆDIATRICIAN (Senior Hospital Medical Officer or Consultant status) for 9 sessions weekly for the Portsmouth Group of hospitals for 2 months from 8th October, 1957. The successful candidate will be required to visit the Isle of Wight Group once weekly. Remuneration in accordance with the terms and conditions of service of hospital medical staff.

Applications, with names and addresses of 2 referees, to the Area Secretary, "Highcroft," Romsey-road, Winchester, by 14th September, 1957.

SOUTH WEST METROPOLITAN REGIONAL HOSPITAL BOARD requires Whole-time CONSULTANT GROUP PATHOLOGIST in the Croydon Group of hospitals, for duties mainly at Mayday Hospital, Thornton Heath, Surrey.

Applications by letter (5 copies), giving date of birth, qualifications, experience, and names of 3 referees, to Secretary (S.1), South West Metropolitan Regional Hospital Board, 11A, Portland-place, W.1, by 14th September, 1957. Applicants may visit hospitals by local arrangement.

SOUTH WEST METROPOLITAN REGIONAL HOSPITAL BOARD requires Whole-time CONSULTANT PATHOLOGIST at the St. Helier Group of hospitals for general clinical pathology. Experience in thoracic surgery pathology an advantage. Duties mainly at St. Helier Hospital, Carshalton, Surrey.

Applications by letter (5 copies), giving date of birth, qualifications, experience, and names of 3 referees, to Secretary (S.1), South West Metropolitan Regional Hospital Board, 11A, Portland-place, W.1, by 14th September, 1957. Applicants may visit hospitals by local arrangement.

WELSH REGIONAL HOSPITAL BOARD. Whole-time Locum Tenens CONSULTANT OBSTETRICIAN AND GYNÆCOLOGIST required mid-Wales Hospital Management Committee area, 26th August–14th September, 1957, inclusive.

Applications, naming 2 referees, to Senior Administrative Medical Officer, Temple of Peace, Cathays Park, Cardiff.

WELSH REGIONAL HOSPITAL BOARD. Whole-time Locum Tenens CONSULTANT (general surgery) required Barry Accident Hospital, 26th August–23rd September, 1957.

Applications, naming 2 referees, to Senior Administrative Medical Officer, Temple of Peace, Cathays Park, Cardiff.

AUSTRALIA. AUSTIN HOSPITAL, Heidelberg. (Situated in Melbourne, Victoria, Australia.) MEDICAL DIRECTOR (Spinal Unit). Applications are invited from medical practitioners, preferably with postgraduate qualifications and preferably with experience in medical rehabilitation of long-term illness, for the above post. The Spinal Unit is newly developed, with 72 Beds, within the Austin Hospital, Heidelberg, as the recognised paraplegic treatment centre for the State of Victoria. Initially the appointment will be for 3 years, but, subject to satisfaction by both parties will be regarded as a permanent appointment. The duties are full-time, with limited right of consultant practice on prescribed terms. Salary will begin at the rate of £3000 (Aust.) p.a., rising by 2 increments to £3250 (Aust.) p.a. Expense of transfer of appointee and his family to Australia will be met by the Hospital. Superannuation and study leave conditions apply.

A schedule giving details of the post will be made available upon inquiry to the Agent-General for Victoria, Victoria House, Melbourne-place, Strand, London, W.C.2.

By order of the Committee of Management,
W. M. POWELL, Manager and Secretary.

Hospital Services : Junior Appointments

BOLINGBROKE HOSPITAL, Wandsworth Common, S.W.11. Locum HOUSE PHYSICIAN, required from 21st September to 4th October, 1957, inclusive.

Apply Hospital Secretary, enclosing copies of 3 recent testimonials.

BOLINGBROKE HOSPITAL, Wandsworth Common, S.W.11. HOUSE SURGEON (resident), vacant 21st September, 1957. Open to registered practitioners and pre-registration candidates.

Apply to Hospital Secretary, enclosing copies of 3 recent testimonials, by 28th August, 1957.

CENTRAL MIDDLESEX HOSPITAL, Park Royal, London, N.W.10. RESIDENT HOUSE OFFICER (post-registration), required in the Obstetric and Gynæcological Department. Post recognised for D.Obst.R.C.O.G. and M.R.C.O.G. Post vacant 1st October, 1957.

Applications, with 2 testimonials, to Medical Director by 24th August.

CENTRAL MIDDLESEX HOSPITAL, Park Royal, London, N.W.10. SENIOR HOUSE OFFICER required for Casualty Department. Successful candidate will work under supervision of Orthopædic and Traumatic Specialist. Appointment for 6 months from 25th September, 1957.

Applications, with names of 2 referees, or copies of 2 testimonials, to Medical Director by 24th August, 1957.

CHARING CROSS HOSPITAL, W.C.2. Locum Registrar in Anæsthesia (full-time), from 16th to 27th September, 1957. Resident at the Obstetric Unit at Kingsbury Maternity Hospital, with duties at other hospitals in the Group. D.A. or the Primary F.F.A.R.C.S. desirable. Possession of a car an advantage.

Application forms obtainable from the undersigned should be returned by 2nd September, 1957.

FRANK HART, Secretary to the Board.

CHARING CROSS HOSPITAL GROUP. Full-time REGISTRAR (resident) in the Department of Psychological Medicine. Duties in Charing Cross Psychiatric Unit at Wembley Hospital, involving modern physical treatments and psychotherapy for inpatients and outpatients.

Applications, on forms obtainable from the undersigned, to be submitted by 31st August, 1957.

FRANK HART,
House Governor and Secretary to the Board.
Charing Cross Hospital, Strand, W.C.2.

CHARING CROSS HOSPITAL GROUP. Wembley HOSPITAL. (134 Beds.) SURGICAL REGISTRAR (resident). Tenable for 1 year in the first instance from 1st October, 1957. Candidates should hold the Diploma of F.R.C.S.

Applications, with copies of testimonials and names of 2 referees, to reach the undersigned by 7th September, 1957.

FRANK HART, Secretary to the Board.
Charing Cross Hospital, Strand, W.C.2.

CONNAUGHT HOSPITAL, Walthamstow, E.17. (123 Beds.) Applications are invited for the post of SECOND CASUALTY OFFICER with duties in the Department of Orthopædic and Traumatic Surgery (Senior House Officer grade). Recognised for F.R.C.S. Salary £819 10s. p.a., less £150 p.a. for board, lodging, &c.

Applications, with full details and copies of 2 recent testimonials, to be sent immediately to Secretary, Forest Group, Hospital Management Committee, Langthorne-road, E.11.

DREADNOUGHT SEAMEN'S HOSPITAL, Greenwich, S.E.10. CASUALTY AND RECEIVING ROOM OFFICER (non-resident) required on 12th September. Post recognised by the Royal College of Surgeons. Salary £819 10s. p.a.

Applications, stating age, nationality, qualifications and experience with the names of 3 recent referees, should be sent to the Secretary at the above address as soon as possible and in any event not later than 24th August.

GUY'S HOSPITAL. York Clinic for Psychological Medi-CINE. Applications are invited for the post of RESIDENT HOUSE PHYSICIAN (Senior House Officer), to commence duties on 1st October, 1957. The post offers good opportunities for postgraduate study. Salary in accordance with the terms and conditions of service for House Officers in the National Health Service. Appointment for 6 months in the first instance, and may be renewed for a further period of 6 months.

Applications, with copies of 2 testimonials, should be sent to the Superintendent, Guy's Hospital, London Bridge, S.E.1, on or before 28th August, 1957.

GUY'S-MAUDSLEY NEUROSURGICAL UNIT. Applications are invited for the resident post of SENIOR HOUSE OFFICER for 6 months, commencing on 1st October, 1957. The unit, which is housed in the Maudsley Hospital, serves Guy's Hospital, and the Bethlem Royal Hospital and the Maudsley Hospital.

Applications should be made within 1 week of the appearance of this advertisement to—

K. J. JOHNSON, House Governor and Secretary.
Maudsley Hospital, Denmark-hill, S.E.5.

HOSPITAL OF ST. JOHN AND ST. ELIZABETH, 60, Grove End-road, London, N.W.8. Locum Tenens Full-time SURGICAL REGISTRAR (Male) required immediately. The possession of the Diploma of Fellow of 1 of the Royal Colleges is essential.

Further particulars may be obtained from the Secretary to whom applications, with names of 3 referees, should be sent.

HIGHLANDS GENERAL HOSPITAL, Winchmore Hill, N.21. SENIOR HOUSE OFFICER (medical), resident, for Chest Unit (100 Beds), vacant 27th September. Duties include tuberculosis work and investigation and treatment of chest diseases under the supervision of the Finchley Chest Clinic, also general medical and geriatric work.

Applications, with copies of 3 testimonials, to Hospital Secretary.

HIGHLANDS GENERAL HOSPITAL. Winchmore Hill, N.21. HOUSE PHYSICIAN, vacant 5th September, 1957. Preference given to applicants seeking pre-registration post under Medical Act, 1950.

Applications, with copies of 3 testimonials and name and address of 1 referee, to Hospital Secretary.

HAMPSTEAD GENERAL HOSPITAL, Haverstock Hill, N.W.3. (ROYAL FREE HOSPITAL GROUP.) Applications are invited from registered medical practitioners for the post of RESIDENT CASUALTY OFFICER (graded as Senior House Officer). Salary £819 10s. p.a. Vacant 1st September, 1957, tenable for a period of 6 months at the Main Outpatients Department, Bayham-street, N.W.1.

Application forms may be obtained from the Secretary, to whom they should be returned, together with copies of 3 recent testimonials, immediately.

KING EDWARD MEMORIAL HOSPITAL, Ealing. North WEST METROPOLITAN REGIONAL HOSPITAL BOARD. REGISTRAR in General Medicine with some pædiatric duties required (non-resident). New appointment. M.R.C.P. an advantage. Candidates may visit Hospital by direct appointment with Hospital Secretary.

Application forms obtainable from, and returnable to, Group Secretary, South West Middlesex Hospital Management Committee, West Middlesex Hospital, Isleworth, by 3rd September.

LAMBETH HOSPITAL, Brook-drive, S.E.11. Applica-tions are invited from pre-registration and registered medical practitioners for the post of RESIDENT HOUSE PHYSICIAN, vacant 1st October, 1957. The successful candidate will be expected to carry out a fortnight's Locum duty from 17th September, 1957.

Application forms from the Acting Physician-Superintendent. A self addressed envelope should be enclosed.

MANOR HOUSE HOSPITAL, Golders Green, N.W.11. (Exempted from National Health Service.) Required, RESIDENT SURGICAL OFFICER (Male). Salary commencing at £852 10s. p.a., less £170 p.a. deducted for emoluments. 6 months appointment, renewable.

Applications, stating age, nationality, qualifications, and surgical or orthopædic experience, with copies of 3 recent testimonials, to Mr. W. F. PENDRILL, Secretary.

MILE END HOSPITAL, Bancroft-road, London, E.1. (484 Beds.) HOUSE PHYSICIAN (pre- or post-registration). Post vacant 8th September, 1957.

Application forms, obtainable from Physician-Superintendent, to be returned by 23rd August, 1957, with copies of not more than 3 testimonials.

NATIONAL HEART HOSPITAL, Westmoreland-street, London, W.1 (with which is associated the Institute of Cardiology). Applications are invited for the post of RESIDENT MEDICAL OFFICER (Male). The appointment is for a period of 6 months from 1st October, 1957, but may be renewed for a further period of 6 months. The status and salary are either that of a Senior House Officer or Registrar and are in accordance with the national terms and conditions of service.

Applications, with copies of 3 recent testimonials, should be sent to me not later than Saturday, 31st August, 1957.

ROBERT G. E. WHITNEY, Secretary to the Board.

NATIONAL HEART HOSPITAL, Maida Moreton, Buck-INGHAM. (Country Branch of the National Heart Hospital.) Applications are invited for the post of RESIDENT MEDICAL OFFICER at the Hospital's Country Branch. The appointment is for a period of 6 months from 1st October, 1957, but may be renewed for a further period not exceeding 6 months. The status of the post is that of a Senior House Officer and the salary is in accordance with the terms and conditions of service. The holder will be expected to attend on 1 day weekly at the Hospital in Westmoreland-street.

Applications, with copies of 3 recent testimonials, should be sent to me at Westmoreland-street, London, W.1, not later than 31st August, 1957.

ROBERT G. E. WHITNEY, Secretary to the Board.

NATIONAL HOSPITALS FOR NERVOUS DISEASES. Applications are invited for the posts of RESIDENT MEDICAL OFFICER and HOUSE PHYSICIAN (resident) at Maida Vale Hospital for Nervous Diseases, London, W.9. Appointments in the first instance for 6 months, renewable. Grading as Senior House Officer or Registrar according to experience. Preference will be given to candidates holding a higher degree and previous neurological experience will be an asset.

Applications, with copies of 3 recent testimonials, should be sent to the Secretary at Maida Vale Hospital not later than 2nd September, 1957.

NEASDEN HOSPITAL, Brentfield-road, Neasden, N.W.10. NORTH WEST METROPOLITAN REGIONAL HOSPITAL BOARD. Whole-time Locum Tenens MEDICAL REGISTRAR (resident) required from 23rd September, 1957, to 6th October, 1957, inclusive. Experience in infectious diseases and children's diseases an advantage. The Hospital is a Regional Centre for poliomyelitis.

Applications to Physician-Superintendent.

NORTH MIDDLESEX HOSPITAL, Edmonton, N.18. SENIOR HOUSE OFFICER in Surgery, resident, required. General surgery, trauma and orthopædics. Post recognised for F.R.C.S. 6 months appointment in the first instance with possible extension to 1 year. Vacant 1st October.

Applications, stating age, nationality, qualifications (Primary Fellowship desirable), experience, with copies of recent testimonials and/or names of 2 referees, to Secretary of Hospital, by 28th August.

NORTH MIDDLESEX HOSPITAL, Edmonton, N.18. HOUSE PHYSICIAN (post-registration), resident, required for 1st October, for 6 months. General medicine.

Applications (in own handwriting), stating age, nationality, experience, with copies of recent testimonials, to Secretary of Hospital, by 28th August.

PRINCE OF WALES'S GENERAL HOSPITAL, N.15. Applications are invited for the appointment of RESIDENT ANÆSTHETIST (Senior House Officer) to the above Hospital for a period of 6 months, vacant 9th October, 1957.

Application form from Secretary, Tottenham Group Hospital Management Committee, The Green, N.15, to be returned by 31st August.

QUEEN ELIZABETH HOSPITAL FOR CHILDREN MANAGEMENT COMMITTEE, Hackney-road, E.2, Shadwell, E.1, and BANSTEAD WOOD, SURREY. 2 RESIDENT MEDICAL OFFICERS (Male or Female) (graded Senior House Officers). 1 at Hackney-road and 1 at Banstead. Applications are invited for the above appointments to become vacant 1st November, 1957. Candidates must have had experience in the treatment of sick children. The appointments will be for 1 year.

Application forms may be obtained from the Secretary at Hackney-road, and should be returned, with copies of not more than 3 testimonials, not later than 29th August, 1957.

QUEEN MARY'S HOSPITAL FOR THE EAST END, Stratford, E.15. SENIOR CASUALTY OFFICER (Male or Female: Senior House Officer grade), for 1 year commencing 3rd October, 1957. Post recognised for F.R.C.S. (i.e., half the year is recognised as casualty and half as general surgery).

Applications, with copies of recent testimonials, to Group Secretary, West Ham Group Hospital Management Committee, Stratford, E.15, by 23rd August, 1957.

ROYAL EYE HOSPITAL. Applications are invited for the post of RESIDENT SENIOR HOUSE OFFICER from 1st October, 1957. The Hospital is recognised for the F.R.C.S. and D.O.

Application forms from the Secretary, Royal Eye Hospital, St. George's-circus, S.E.1, not later than 30th August, 1957.

ROYAL FREE HOSPITAL. Applications are invited for the post of RESIDENT SENIOR HOUSE OFFICER to the Radiotherapy Department. Applicants should be registered medical practitioners, and the appointment is suitable for a candidate doing a postgraduate course in radiotherapy. The appointment is for 1 year in the first instance. Salary and conditions of service in accordance with the scale laid down by the Ministry of Health for Senior House Officers. Duties to commence 1st October, 1957.

Application forms may be obtained from the Hospital Secretary, Royal Free Hospital, Gray's Inn-road, W.C.1, to whom they should be returned not later than 4th September, 1957.

ROYAL FREE HOSPITAL GROUP. Applications are invited for the post of SENIOR REGISTRAR to the Anæsthetic Department, recognised within Senior Registrar establishment, duties to commence 1st October, and the post is for 1 year in the first instance. Salary in accordance with the scale laid down by the Ministry of Health for Senior Registrars.

Applications, together with the names of 3 referees, should be sent to the Secretary to the Board of Governors, Royal Free Hospital, Gray's Inn-road, W.C.1, not later than 31st August, 1957.

ROYAL FREE HOSPITAL. Applications are invited from registered Men or Women practitioners for the whole-time non-resident posts of 2 REGISTRARS in Clinical Pathology. Both appointments for 1 year in the first instance, from 1st October, 1957. 1 post will be almost entirely engaged in chemical pathology and the other in hæmatology: previous clinical pathology experience essential.

Applications should be sent to the Secretary to the Board of Governors, Royal Free Hospital, London, W.C.1, not later than 1st September, 1957.

ROYAL MARSDEN HOSPITAL, Fulham-road, S.W.3. Applications are invited for 2 full-time posts of REGISTRAR in the Radiotherapy Department. Salary £935 a year. Candidates not holding a Diploma in Medical Radiology will be considered, especially if they have a higher qualification in medicine or surgery.

Forms of application are obtainable from the House Governor, to whom applications, together with the names of 3 referees, should be sent by 30th August, 1957.

ROYAL MARSDEN HOSPITAL, Fulham-road, S.W.3. Applications are invited from registered medical practitioners for the post of HOUSE SURGEON (resident). Salary £577 10s. a year. The post is tenable for 6 months from 3rd November, 1957.

Forms of application are obtainable from the House Governor, to whom applications, together with copies of 3 recent testimonials, should be sent, not later than 30th August, 1957.

ROYAL NORTHERN HOSPITAL. (279 Beds.) North WEST METROPOLITAN REGIONAL HOSPITAL BOARD. REGISTRAR required in the Orthopædic and Fracture Department of the above Hospital. The Department has a very large fracture clinic. Candidates may visit the Hospital by direct appointment.

Application forms obtainable from, and returnable to, the Secretary, Royal Northern Hospital, Holloway-road, London, N.7, by 27th August, 1957.

ST. THOMAS'S HOSPITAL AND THE HOSPITAL FOR SICK CHILDREN, Great Ormond-street, London, W.C.1. There will be a vacancy on 1st November, 1957, for a SENIOR REGISTRAR in Plastic Surgery. The post is full-time and non-resident. The successful candidate will be required to devote 6 sessions per week to St. Thomas's Hospital and 5 sessions to The Hospital for Sick Children.

Further particulars and forms of application which must be returned not later than 27th August, 1957, may be obtained from the undersigned.

H. F. RUTHERFORD, House Governor and Secretary.

The Hospital for Sick Children.

ST. THOMAS'S HOSPITAL, London, S.E.1. Locum SENIOR HOUSE OFFICER to the Department of Physical Medicine required immediately until the end of October.

Applications, naming 2 referees, to the Clerk of the Governors by 23rd August, 1957.

ST. THOMAS'S HOSPITAL, London, S.E.1. Senior REGISTRAR in Dental Surgery for a period of 1 year in the first instance from 1st November, 1957, to carry out 5 half-day sessions per week. Medical or other additional qualifications will be an advantage.

Applications, naming 2 referees, to the Clerk of the Governors by 30th August, 1957.

ST. THOMAS'S HOSPITAL, London, S.E.1. Registrar to the Skin Department for a period of 1 year in the first instance.

Applications, naming 2 referees, to the Clerk of the Governors by 30th August, 1957.

ST. GEORGE'S HOSPITAL, S.W.1. Applications are invited for the whole-time post of SENIOR REGISTRAR to the Department of Radiology. This post is non-resident and the holder will work mainly in the Neuro-radiological Department at St. George's Hospital (Atkinson Morley's Hospital Branch). The successful candidate will be required to take up duty as soon as possible after 1st September, 1957.

Applications, stating age, education, qualifications, and experience, together with the names of 2 referees, should reach the undersigned not later than 31st August, 1957.

P. H. CONSTABLE, House Governor.

ST. GEORGE'S HOSPITAL, S.W.1. Applications are invited for the post of REGISTRAR to the Department of Obstetrics and Gynæcology. Candidates should be Fellows of the Royal College of Surgeons or Members of the Royal College of Obstetricians and Gynæcologists. The post is non-resident, and the successful candidate will be required to take up duty as soon as possible.

Applications, stating age, education, qualifications and experience, together with the names of 2 referees, should reach the undersigned not later than 7th September, 1957.

P. H. CONSTABLE, House Governor.

ST. GEORGE'S HOSPITAL, S.W.1. Applications are invited for the post of FIRST ASSISTANT in General Medicine, in the grade of Registrar, in the St. George's Hospital Group. The appointment will be for 1 year, from 1st October, 1957. Membership of the Royal College of Physicians is desirable.

Applications, stating age, education, qualifications, experience, and the names of 2 referees, should reach the undersigned not later than 24th August, 1957.

P. H. CONSTABLE, House Governor.

ST. GEORGE'S HOSPITAL, S.W.1, AND SOUTH-AMPTON HOSPITAL GROUP. (Joint appointment.) Applications are invited for the post of SENIOR REGISTRAR to the Department of Anæsthetics. Candidates should hold the Diploma of Fellowship of the Faculty of Anæsthetists. This is a full-time appointment, non-resident except for emergency duties, and the successful candidate will be required to take up duty on 1st November, 1957. Part of the normal period as Senior Registrar will be served at St. George's Hospital, and part with the Southampton Group of hospitals. The initial period will be spent at the Southampton Group of hospitals, where a furnished flat is available if required.

Applications, stating age, education, qualifications and experience, together with the names of 2 referees, should reach the undersigned not later than 7th September, 1957.

P. H. CONSTABLE, House Governor.

ST. GILES' HOSPITAL, Camberwell, S.E.5. Applications invited for appointment as SENIOR HOUSE OFFICER (general medical duties), vacant from 22nd September. Resident post.

Apply, giving age and details of qualifications and previous posts, with copy testimonials or names of 2 referees, to Group Secretary, Camberwell Hospital Management Committee, Dulwich Hospital, East Dulwich-grove, S.E.22, not later than 29th August, 1957.

ST. GILES' HOSPITAL, Camberwell, S.E.5. Applications invited for appointment as SENIOR HOUSE OFFICER (obstetrics and gynæcology), vacant from 16th September. Resident post.

Apply, giving age, qualifications and previous posts, with copy testimonials or names of referees, to Group Secretary, Camberwell Hospital Management Committee, Dulwich Hospital, East Dulwich-grove, S.E.22, not later than 29th August.

ST. MARK'S HOSPITAL, City-road, London, E.C.1. Applications invited from Senior Registrars who have completed their training or Registrars who have completed their appointments for the post of RESIDENT SURGICAL OFFICER. Part of time non-resident by arrangement. Salary at the rate of £1540 or £1061 10s. respectively. Appointment tenable for 6 months from 1st October with possibility of further extension for 6 months.

Applications, stating age, qualifications, experience, names of 2 referees, to Secretary, Board of Governors, The Hammersmith, West London and St. Mark's Hospitals, Ducane-road, London, W.12, by 24th August.

ST. MARY'S HOSPITAL, Paddington, W.2. Applications are invited from suitably qualified practitioners for the post of non-resident Whole-time REGISTRAR in General Medicine. The successful candidate will be required to undertake work in the Casualty and Outpatient Departments as well as having certain inpatient duties. The appointment will be for a first period of 12 months as from 1st October, 1957.

Applications, stating nationality, date of birth, permanent address, qualifications with dates, details and National Health Service gradings of previous and present appointments, together with the names and addresses of 3 referees, should reach ALAN POWDITCH, House Governor, not later than 26th August, 1957.

THE HOSPITAL FOR SICK CHILDREN, Great Ormond-street, London, W.C.1. Applications are invited for the post of Whole-time SENIOR REGISTRAR to the E.N.T. Department, falling vacant on 1st November, 1957.

Further particulars and form of application, which must be returned not later than Monday, 9th September, 1957, are obtainable from the undersigned.

H. F. RUTHERFORD, House Governor and Secretary.

THE HOSPITAL FOR SICK CHILDREN, Great Ormond-street, London, W.C.1. There will be vacancies for the following Senior House Officers :—

1 HOUSE PHYSICIAN—on 15th November, 1957.
1 HOUSE SURGEON to the Orthopædic and Plastic Departments—on 15th November, 1957.

Further particulars and form of application, which must be returned not later than 9th September, 1957, are obtainable from the undersigned.

H. F. RUTHERFORD, House Governor and Secretary.

THE HOSPITAL FOR SICK CHILDREN, Great Ormond-street, London, W.C.1. There will be a vacancy in October, 1957, for a SENIOR REGISTRAR in Anæsthetics. The post is full-time and non-resident. The successful candidate will be required to rotate with a Senior Anæsthetic Registrar at University College Hospital, spending 6 months at a time at each hospital.

Further particulars and forms of application which must be returned not later than 2nd September, 1957, may be obtained from the undersigned.

H. F. RUTHERFORD, House Governor and Secretary.

TOOTING BEC HOSPITAL, Tooting Bec-road, S.W.17. (Mental hospital, over 2000 Beds.) Temporary JUNIOR HOSPITAL MEDICAL OFFICER (resident or non-resident) required to commence duty 30th September, 1957. The Hospital is within easy access of teaching centres in London. Offers good opportunities for study for higher qualifications.

Applications, with names of 2 referees, to be sent to the Physician-Superintendent within 2 weeks of the appearance of this advertisement.

WANSTEAD HOSPITAL, Hermon Hill, E.11. (191 Beds.) Applications are invited for the post of RESIDENT ANÆSTHETIST (graded Senior House Officer), vacant 12th September, 1957. Salary £819 10s. p.a., less £150 p.a. for board, lodging, &c. Recognised for the F.F.A.R.C.S. and D.A.

Applications, stating age, qualifications and experience, together with copies of 2 recent testimonials, to be sent immediately to Secretary, Forest Group Hospital Management Committee, Langthorne-road, E.11.

WEST HAM GROUP HOSPITAL MANAGEMENT COMMITTEE, Stratford, E.15. ANÆSTHETIST (Resident Senior House Officer grade) for 12 months commencing as soon as possible. 6 months at Queen Mary's Hospital for the East End and 6 months at East Ham Memorial Hospital. Combined post recognised for D.A. and F.F.A.R.C.S.

Applications, with names of 3 referees, to Group Secretary, West Ham Group Hospital Management Committee, Stratford, E.15, by 21st August, 1957.

WESTMINSTER HOSPITAL, St. John's-gardens, S.W.1. Applications invited for post of RESIDENT CASUALTY OFFICER (Senior House Officer grade) with duties as House Physician in Skin Department for 1 year from 1st October, 1957. Board and lodging £150 p.a.

Applications (11 copies), with names of 2 referees, to House Governor by 31st August.

WHIPPS CROSS HOSPITAL, London, E.11. Applications are invited for the post of Pre-registration HOUSE SURGEON (orthopædics), vacant 1st September, 1957.

Application forms from the Hospital Secretary to be returned by 26th August, 1957.

WHITTINGTON HOSPITAL, London, N.19. Locum Tenens ORTHOPÆDIC REGISTRAR required from 1st September, 1957.

Write or call Medical Superintendent (ARChway 3070, Extension 440).

ACCRINGTON. VICTORIA HOSPITAL. (114 Beds.) BLACKBURN AND DISTRICT HOSPITAL MANAGEMENT COMMITTEE. HOUSE SURGEON required for 6th September, 1957. Post recognised for F.R.C.S. and approved for pre-registration purposes.

Applications to Group Secretary, Hospital Management Committee Office, Royal Infirmary, Blackburn.

AMERSHAM AND HIGH WYCOMBE HOSPITALS. Locum REGISTRAR in Medicine required for holiday period 15th September–6th October (inclusive) to take charge of 44 Beds ; 5 outpatient sessions weekly.

Applications to Group Secretary, High Wycombe Hospital Management Committee, St. Mary's-street, High Wycombe.

ASHINGTON HOSPITAL, Ashington. (55 Beds.) WANSBECK HOSPITAL MANAGEMENT COMMITTEE. RESIDENT SURGICAL OFFICER (Junior Hospital Medical Officer) required for locum tenens duties, 23rd August–24th September, approximately.

Apply Group Secretary, Wansbeck Hospital Management Committee, 12, Stanley-street, Blyth, Northumberland.

ASHTON, HYDE AND GLOSSOP HOSPITAL MANAGEMENT COMMITTEE. SENIOR HOUSE OFFICER (general surgery) required at Ashton-under-Lyne General Hospital. Recognised under F.R.C.S. regulations. Vacant September.

Applications, with copies of 2 testimonials, to Group Secretary, Ashton-under-Lyne General Hospital, Ashton-under-Lyne, Lancs.

BANGOR. ST. DAVID'S HOSPITAL. (136 Beds. Specialist Hospital for Obstetrics, Gynæcology and Pædiatrics.) Part I Midwifery Training School. Applications are invited for the post of RESIDENT SENIOR HOUSE OFFICER (obstetrics) in the Gynæcological and Obstetrical Department of the above Hospital. Previous obstetrical experience essential. The post is recognised by the Royal College of Obstetricians and Gynæcologists for the Membership examination. Salary according to scale.

Applications, stating age, qualifications and experience, together with copies of 3 recent testimonials, to be forwarded to the Group Secretary, Caernarvon and Anglesey Hospital Management Committee, Plas Gwyn, Ffriddoedd-road, Bangor, within 10 days of the appearance of this advertisement.

BARNSTAPLE. NORTH DEVON INFIRMARY. (105 Beds.) HOUSE SURGEON (pre-registration) required. Post vacant 4th September, 1957.

Applications to Group Secretary, North Devon Hospital Management Committee, 19, Alexandra-road, Barnstaple.

BARNSTAPLE. NORTH DEVON INFIRMARY. (105 Beds.) SENIOR HOUSE OFFICER required, whose duties will be mainly casualty. Post tenable for 1 year. Small furnished flat available.

Applications to Group Secretary, North Devon Hospital Management Committee, 19, Alexandra-road, Barnstaple.

BASINGSTOKE, HAMPSHIRE. PARK PREWETT AND PINEWOOD HOSPITALS. Applications are invited for the appointment of JUNIOR HOSPITAL MEDICAL OFFICER at the Group. The admission-rate is nearly 1500 annually, over one-third being infirmal. All modern treatments are used and opportunity will be given for varied experience in all branches of psychiatry. The Hospital is recognised by the London University and Royal Colleges for the D.P.M. Salary and conditions of service in accordance with national scale. Residential accommodation is available to a single person at a charge of £170 p.a.

Applications, with full particulars and names and addresses of 2 referees, should be sent to the Group Secretary, Park Prewett Hospital, Basingstoke, as soon as possible.

BEVERLEY, YORKSHIRE. WESTWOOD HOSPITAL. (229 acute beds.) HOUSE SURGEON (first, second or third post), vacant soon. General surgical duties, some orthopædics. Offering good opportunities for general experience in busy acute general hospital. Recognised for F.R.C.S. Approved pre-registration post. Married quarters may be available.

Applications to Group Secretary.

BEVERLEY, YORKSHIRE. WESTWOOD HOSPITAL. (229 acute beds.) ORTHOPÆDIC HOUSE SURGEON (first, second or third post), vacant now. Offers good opportunity for general experience in busy acute general hospital. Approved pre-registration post. Fully qualified practitioners may apply. Recognised for F.R.C.S.

Apply Group Secretary.

BEXHILL HOSPITAL, Bexhill-on-Sea. (62 Beds.) HOUSE SURGEON (resident) required. Pre-registration post vacant now. National scale of salary.

Apply to Hospital Administrator.

BIRMINGHAM, 18. DUDLEY ROAD HOSPITAL. E.N.T. DEPARTMENT. HOUSE SURGEON (resident), vacant 18th September, 1957. Recognised for D.L.O. Busy Hospital with 780 Beds with approximately 50 E.N.T. beds. Candidates with previous experience in E.N.T. work considered for appointment as Senior House Officer.

Applications, with copies of 2 recent testimonials, to the Group Secretary.

BIRMINGHAM, 18. DUDLEY ROAD HOSPITAL. Junior PATHOLOGIST (Junior Hospital Medical Officer), non-resident, vacant 1st October. Recognised for Dip. Pathology. Post offers wide experience in all branches.

Detailed applications to Group Secretary.

BIRMINGHAM REGIONAL HOSPITAL BOARD.

(1) **Coventry No. 20 Group, Coventry and Warwickshire Hospital, Coventry**

REGISTRAR (general surgery) for Gulson Hospital, Coventry (312 Beds). Resident. Recognised F.R.C.S. Experience specialty essential. Higher qualification desirable. Vacant 8th September.

(2) **Dudley, Stourbridge Group, The Guest Hospital, Dudley**

REGISTRAR (general surgery) for The Guest Hospital, Dudley (171 Beds). Experience specialty essential. Higher qualification desirable. Resident.

(3) **Mid-Worcestershire Group, Birmingham-road, Bromsgrove**

REGISTRAR (casualty) for Kidderminster and District General Hospital (112 Beds) required also to deputise for Surgical Registrar. Experience specialty essential. Higher qualification desirable. Resident or non-resident.

(4) **Birmingham (Selly Oak) Group, Oak Tree-lane, Birmingham, 29**

REGISTRAR (E.N.T.) for Selly Oak Hospital (1055 Beds) (42 Beds E.N.T. Department). Non-resident. Experience specialty and higher qualification an advantage.

(5) **Shrewsbury Group, Royal Salop Infirmary, Shrewsbury**

REGISTRAR (chest diseases) (Salop Area). Duties at Chest Clinics (mainly Shrewsbury and Wellington) and group hospitals (mainly Wellington, Cross Houses and Shirlett Sanatorium). Previous experience essential. Vacant 1st October.

(6) **South Warwickshire Group, 50, Holly-walk, Leamington Spa**

REGISTRAR (psychiatry). Outpatients (adults and children) at Coventry, Nuneaton and Rugby Hospitals (7 sessions) : 4 inpatient sessions at Central Hospital, near Warwick, with E.E.G. Department, occupational therapy and all modern treatments, also Neurosis Unit now excluded from the Lunacy and Mental Treatment Acts. House available.

Application forms from Group Secretaries to be returned by 26th August, 1957.

BIRMINGHAM. THE UNITED BIRMINGHAM HOSPITALS, THE CHILDREN'S HOSPITAL, Ladywood-road, BIRMINGHAM, 16. Applications are invited for the post of SURGICAL REGISTRAR (non-resident), vacant 29th September, 1957. Excellent opportunities exist for performance of pædiatric surgery in close association with the Consultant Surgeons of the Teaching Hospital. Preference will be given to candidates holding a higher qualification. Residence in the Hospital will be required when the Resident Surgical Officer is absent.

Forms of application may be obtained from the House Governor and should be returned not later than 7th September, 1957. G. A. PHALP, Secretary to the Board of Governors.

BIRMINGHAM. THE UNITED BIRMINGHAM HOSPITALS. THE BIRMINGHAM MATERNITY HOSPITAL. Applications are invited from registered medical practitioners for the post of RESIDENT OBSTETRIC HOUSE SURGEON, vacant 1st November, 1957. The appointment is recognised for the M.R.C.O.G. and D.Obst.R.C.O.G.

Application forms obtainable from the House Governor, the Birmingham and Midland Hospitals for Women, Showell Green-lane, Sparkhill, Birmingham, 11, to be returned not later than 2nd September, 1957. G. A. PHALP, Secretary.

BLACKBURN AND DISTRICT HOSPITAL MANAGEMENT COMMITTEE. SENIOR HOUSE OFFICER (pathology) required for duties at Royal Infirmary, Blackburn (Group Laboratory), but may also be required for duties at Queen's Park Hospital, Blackburn, and Victoria Hospital, Accrington, at Consultant's discretion. Recognised for D.Path. Post vacant 2nd October, 1957.

Applications, with names of 2 referees, to Group Secretary, Hospital Management Committee Office, Royal Infirmary, Blackburn.

BLACKBURN. QUEEN'S PARK HOSPITAL (640 general beds.) BLACKBURN AND DISTRICT HOSPITAL MANAGEMENT COMMITTEE. SENIOR HOUSE OFFICER (medicine) required 16th September, for acute Medical Unit.

Applications, with names of 2 referees, to Group Secretary, Hospital Management Committee Office, Royal Infirmary, Blackburn.

BLACKPOOL VICTORIA HOSPITAL. Senior House OFFICER (paediatrics) required. Post is recognised for D.C.H. and is vacant on 1st October.

Applications, stating the names and addresses of 2 referees, should be sent to the Group Secretary, Victoria Hospital, Blackpool.

BOLTON AND DISTRICT HOSPITAL MANAGEMENT COMMITTEE. RESIDENT ANÆSTHETIST (Senior House Officer grade). Main duties at Bolton District General Hospital and Bolton Royal Infirmary. Vacant mid-September, tenable for 12 months and recognised for the D.A. and F.F.A.R.C.S.

Applications, stating age, nationality, qualifications, experience, and the names of 2 referees, to Group Secretary, The Royal Infirmary, Bolton.

BRAINTREE, ESSEX. BLACK NOTLEY HOSPITAL. (516 Beds.) Applications invited for the following posts :—

HOUSE OFFICER (orthopædic surgery). Duties include care of cases from London Hospital Orthopædic Department. First, second, third or pre-registration post, tenable for 6 months. Recognised for F.R.C.S.

Locum ORTHOPÆDIC REGISTRAR, with some duties at the London Hospital, from 24th August to 6th October.

Applications, with copies of 3 testimonials, to Group Secretary, Colchester Group Hospital Management Committee, 14, Pope's-lane, Colchester, Essex.

BRISTOL. COSSHAM AND FRENCHAY HOSPITAL MANAGEMENT COMMITTEE. SENIOR HOUSE OFFICER required for the Department of Thoracic Surgery (120 Beds) at Frenchay Hospital.

Apply to Group Secretary, Frenchay Hospital, Bristol, giving age and experience and quoting 2 referees.

BROMLEY HOSPITAL, Kent. Senior House Officer (anæsthetics), qualified minimum 1 year, for duty at Group hospitals, required end of September. Recognised for D.A. and F.F.A.R.C.S. Resident, or non-resident if local.

Apply, naming 3 referees, to Administrative Officer.

BOURNEMOUTH. ROYAL VICTORIA HOSPITAL, Shelley-road. BOURNEMOUTH AND EAST DORSET HOSPITAL MANAGEMENT COMMITTEE. Applications are invited for the appointment of GENERAL HOUSE SURGEON. The appointment, which becomes vacant on 7th October, 1957, is recognised for the F.R.C.S. examination and for pre-registration purposes.

Applications to the Hospital Secretary.

BURTON GENERAL HOSPITAL AND ANDRESSEY HOSPITAL, BURTON-ON-TRENT. HOUSE SURGEON (gynæcological and obstetrics) required immediately at above Hospital. Post recognised for pre-registration purposes.

Apply Group Secretary.

BURTON-ON-TRENT. THE GENERAL HOSPITAL. HOUSE SURGEON (general and pre-registration) required at the above Hospital as from 1st September, 1957. Post recognised for F.R.C.S.

Applications to Group Secretary as soon as possible.

BURTON-ON-TRENT. GENERAL HOSPITAL. Junior HOSPITAL MEDICAL OFFICER ANÆSTHETIST required at the above Hospital.

Applications to Group Secretary, General Hospital, Burton-on-Trent, as soon as possible.

BURTON-ON-TRENT (near). BRETBY HALL ORTHOPÆDIC HOSPITAL. (78 available orthopædic beds.) SHEFFIELD REGIONAL HOSPITAL BOARD. Whole-time RESIDENT REGISTRAR (orthopædics) required for inpatient and operative work with children and adults. Hospital quarters available. Duties include certain outpatient responsibilities at Derbyshire Royal Infirmary. Appointment for 1 year in first instance.

Apply to Secretary, Sheffield Regional Hospital Board, Old Fulwood-road, Sheffield, by 26th August, 1957, giving age, nationality, qualifications, present and previous appointments with dates, naming 3 referees.

CARSHALTON, SURREY. ST. HELIER HOSPITAL (733 Beds.) ANÆSTHETIC REGISTRAR. Post vacant 25th October. Hospital recognised for F.F.A.R.C.S. and D.A.

Forms of application to be returned by 31st August may be obtained from the Group Secretary at above address.

CARSHALTON. QUEEN MARY'S HOSPITAL FOR CHILDREN. Locum ANÆSTHETIC REGISTRAR required from 16th September, 1957, for an indefinite period.

Apply Group Secretary (Wallington 6635, Ext. 18).

CAERPHILLY HOSPITAL. (226 Beds for acute general medicine and surgery.) Pre-registration HOUSE OFFICER (orthopædics and general surgery) required at above Hospital.

Apply immediately, with names of referees, to the Group Secretary, Rhymney and Sirhowy Valleys Hospital Management Committee, Central Offices, Caerphilly-road, Ystrad Mynach, Glam.

CANTERBURY (near). ST. AUGUSTINE'S HOSPITAL, CHARTHAM, near CANTERBURY. JUNIOR HOSPITAL MEDICAL OFFICER (Male or Female) required at this Mental Hospital. Salary scale £852 10s.–£1182 10s. Quarters available or modern house for married man. The post offers experience in all branches of psychiatry, including all forms of modern treatment and out-patients clinics. The Hospital has a high admission-rate and is recognised for the D.P.M.

Apply to the Physician-Superintendent.

CARDIFF. ST. DAVID'S HOSPITAL. Senior House OFFICER required for Accident Unit at above Hospital.

Form of application from Group Secretary, Cardiff Hospital Management Committee, 44, Cathedral-road, Cardiff.

CARLUKE, LANARKSHIRE. LAW HOSPITAL. Applications are invited for the following resident posts (pre- or post-registration) for the 6 months commencing immediately.

HOUSE OFFICER (orthopædic).

HOUSE OFFICER (surgical).

Applications, stating age, qualifications and previous experience, together with the names of 2 referees, should be submitted to the Group Medical Superintendent, Law Hospital, Carluke.

CHELTENHAM GENERAL EYE AND CHILDREN'S HOSPITAL. (CHILDREN'S DEPARTMENT.) Applications are invited for the post of RESIDENT MEDICAL OFFICER (Senior House Officer grade) for the Children's Department (54 Beds) vacant mid-September. The appointment which is recognised for candidates entering for the D.C.H. offers scope for wide experience in all departments of pædiatrics, surgical cases, and attendance at Outpatient Departments at the General Hospital. Previous hospital experience in pædiatrics is desirable.

Applications, together with copies of 3 testimonials, should be addressed to S. T. DAVIS, Group Secretary.

General Hospital, Cheltenham.

CHELTENHAM GENERAL HOSPITAL. (220 Beds.) HOUSE SURGEON (pre- or post-registration) required mid-September. The post offers a wide experienco in general surgery, gynæcology, and orthopædic surgery. Post recognised for the F.R.C.S.

Apply Secretary, General Hospital, Cheltenham.

CHESTERFIELD ROYAL HOSPITAL. Casualty Officer (House Officer or Senior House Officer) required 30th September, 1957. Post recognised for the F.R.C.S. and pre-registration purposes.

Apply, with copies of 2 testimonials, to—

M. H. BOONE, Group Secretary.

CHICHESTER. ST. RICHARD'S HOSPITAL. (400 Beds.) Required, SENIOR HOUSE OFFICER to the General and the Medical and Surgical Chest Units. Post becomes vacant at the end of September.

Applications, stating age, qualifications and experience and giving names of 2 persons to whom reference may be made, should be sent to the Surgeon-Superintendent.

COLCHESTER. ESSEX COUNTY HOSPITAL. (185 Beds.) Applications invited for post of HOUSE OFFICER (surgical). First, second, third or pre-registration post, tenable for 6 months. Recognised for F.R.C.S.

Applications, with copies of 3 testimonials, to Group Secretary, Colchester Hospital Management Committee, 14, Pope's-lane, Colchester, Essex.

COULSDON, SURREY. CANE HILL HOSPITAL. Cane HILL HOSPITAL MANAGEMENT COMMITTEE. SOUTH WEST METROPOLITAN REGIONAL HOSPITAL BOARD. REGISTRAR in Psychiatry, whole-time, resident (if unmarried) or non-resident. The Hospital has 5 outpatient clinics and undertakes post-graduate teaching in association with the Institute of Psychiatry. Every facility will be given for further study. Candidates may visit the Hospital by arrangment with the Physician-Superintendent.

Application forms, returnable within 14 days, may be obtained from the Group Secretary.

CREWE AND DISTRICT MEMORIAL HOSPITAL. (108 Beds Acute, and Continuation 32 Beds.) 2 Pre-registration HOUSE OFFICERS (surgical) required. Approved for F.R.C.S. Salary and conditions in accordance with Whitley Council scale. The appointments may be followed by second posts.

Apply immediately, stating age, qualifications, &c., with names of 2 referees, to the Group Secretary, South Cheshire Hospital Management Committee, Barony Hospital, Nantwich, Cheshire.

CREWE AND DISTRICT MEMORIAL HOSPITAL. (108 Beds Acute, and Continuation 32 Beds.) SENIOR HOUSE OFFICER (casualty). Modern well-equipped department. Whitley Council salary scale and conditions of service.

Applications, stating age, qualifications, &c., with names of 2 referees, to be sent as soon as possible to the Group Secretary, South Cheshire Hospital Management Committee, Barony Hospital, Nantwich, Cheshire.

CREWE AND DISTRICT MEMORIAL HOSPITAL. (108 Beds Acute, and Continuation 32 Beds.) JUNIOR HOSPITAL MEDICAL OFFICER (anæsthetics), temporary or permanent, D.A. preferred. New operating suite. Duties chiefly at general hospital and a Maternity Unit at another hospital. Hospital approved for D.A. Salary and conditions as per regulations.

Applications, giving age, details of experience, and names of 3 referees, to be sent immediately to Group Secretary, South Cheshire Hospital Management Committee, Barony Hospital, Nantwich, Cheshire.

CREWE AND DISTRICT MEMORIAL HOSPITAL. REGISTRAR (Orthopædic Department) required. Modern Theatres and Accident Department, incorporating every facility. Full traumatic and orthopædic service being developed. Now vacant. Salary and conditions as per regulations.

Applications, stating age, qualifications and experience, together with names of 3 referees, to Group Secretary, South Cheshire Hospital Management Committee, Barony Hospital, Nantwich.

CREWE AND DISTRICT MEMORIAL HOSPITAL. (108 Beds Acute, and Continuation 32 Beds.) Locum SURGICAL REGISTRAR required immediately for 3 weeks holiday duty. Salary and conditions in accordance with Whitley Council scale.

Applications, stating age, qualifications, &c., with names of 2 referees, to be sent as soon as possible to the Group Secretary, South Cheshire Hospital Management Committee, Barony Hospital, Nantwich, Cheshire.

CUCKFIELD HOSPITAL, Cuckfield, near Haywards HEATH, SUSSEX. RESIDENT JUNIOR HOUSE OFFICER (medical), post now vacant. Health Service terms and conditions.

Applications, stating age, nationality, qualifications and experience, with names of 2 referees, to Group Secretary, Mid-Sussex Hospital Management Committee.

DARLINGTON (near). AYCLIFFE HOSPITAL, HEIGHINGTON, near DARLINGTON, CO. DURHAM. AYCLIFFE HOSPITAL MANAGEMENT COMMITTEE. Applications are invited for the post of JUNIOR HOSPITAL MEDICAL OFFICER at the above Hospital for mental defectives (664 Beds). A suitable house is available for a married man at a reasonable charge, and resident accommodation can also be provided for an unmarried medical officer. The Hospital is a modern one and approved for the D.P.M. examination of the Durham University and Conjoint Examining Board. Salary will be in accordance with the terms and conditions of hospital medical and dental staffs—i.e., £852 10s.–£55–£1182 10s. p.a.

Candidates are invited to visit the Hospital by arrangement with the Medical Superintendent to whom applications should be addressed, together with the names and addresses of 2 referees, not later than 7th September, 1957.

T. H. ALLAN, Group Secretary.

DERBY. CITY HOSPITAL. Derby Area No. 1 Hospital MANAGEMENT COMMITTEE. Applications are invited for the post of HOUSE PHYSICIAN (pre-registration) or SENIOR HOUSE OFFICER (medical). Post vacant 11th September.

Applications, stating full details, together with copies of 2 recent testimonials, should be sent to the Medical Superintendent, City Hospital, Derby, as soon as possible.

DERBY. CITY HOSPITAL (Obstetrical Department— 76 Beds.) DERBY AREA NO. 1 HOSPITAL MANAGEMENT COMMITTEE. Applications are invited for the following posts :—

OBSTETRIC HOUSE SURGEON (pre-registration) or SENIOR HOUSE OFFICER for duties at the Derby City Hospital (76 Beds) and some duties at the Queen Mary Maternity Home (36 Beds). Vacant 1st October, 1957.

OBSTETRIC HOUSE SURGEON (Senior House Officer) for duties at the Derby City Hospital. This post is recognised by the Royal College of Obstetricians for the M.R.C.O.G., and the D.Obst.R.C.O.G. Vacant 1st October, 1957.

Applications, stating age, qualifications and experience, with copies of 2 testimonials, should be sent to the Medical Superintendent, City Hospital, Derby.

DERBY. DERBYSHIRE ROYAL INFIRMARY (416 Beds), DERBY CITY HOSPITAL (260 Beds). (Posts recognised for training for D.A. and F.F.A.R.C.S.) SHEFFIELD REGIONAL HOSPITAL BOARD. 2 Whole-time RESIDENT REGISTRARS (anæsthetics) required for the above hospitals. Duties also at other hospitals in the Group. These posts offer special experience in neuro and orthopædic surgery and obstetrics. Appointment for 1 year in first instance.

Apply to Secretary, Sheffield Regional Hospital Board, Old Fulwood-road, Sheffield, by 26th August, 1957, giving age, nationality, qualifications, present and previous appointments with dates, naming 3 referees.

DERBY. DERBYSHIRE HOSPITAL FOR WOMEN, FRIAR GATE, DERBY. HOUSE SURGEON (pre-registration) or SENIOR HOUSE OFFICER (gynæcology). 2 vacancies, 1 for 10th September, the other 27th September. Recognised for M.R.C.O.G. in gynæcology only.

Apply, stating full details and for which vacancy, with copies of 2 recent testimonials, to Group Secretary, Derbyshire Royal Infirmary, Derby.

DONCASTER ROYAL INFIRMARY. (330 Beds.) SHEFFIELD REGIONAL HOSPITAL BOARD. Whole-time RESIDENT MEDICAL REGISTRAR required on 1st October. Appointment for 1 year in first instance.

Apply to Secretary, Sheffield Regional Hospital Board, Old Fulwood-road, Sheffield, by 26th August, 1957, giving age, nationality, qualifications, present and previous appointments with dates, naming 3 referees.

EBBW VALE HOSPITAL. (General Beds 71—Maternity 15.) Applications are invited for the appointment of SENIOR HOUSE OFFICER. The Hospital is an active Surgical Unit and the medical staff consist of a Resident Surgeon and Junior Hospital Medical Officer and visiting Orthopædic, Gynæcological, and Ophthalmic Surgeons. The tenure of appointment shall be for a period of 12 months.

Apply, giving full details and references, to the Group Secretary, North Monmouthshire Hospital Management Committee, Nevill Hall, Abergavenny, Mon.

EDGWARE GENERAL HOSPITAL, Edgware, Middlesex. RESIDENT HOUSE SURGEON for above Hospital. Post vacant 6th October. 1957. 6 months appointment. Recognised for F.R.C.S. and pre-registration purposes.

Applications, stating age, qualifications, experience and enclosing copies of up to 3 recent testimonials, to Medical Director of Hospital by 31st August, 1957.

EDGWARE GENERAL HOSPITAL, Edgware, Middlesex. RESIDENT OBSTETRIC HOUSE SURGEON for above Hospital. Post vacant 18th September, 1957. 6 months appointment. Recognised for M.R.C.O.G. and pre-registration purposes.

Applications, stating age, qualifications, experience and enclosing copies of up to 3 recent testimonials, to Medical Director of Hospital by 31st August, 1957.

EDGWARE GENERAL HOSPITAL, Edgware, Middlesex. RESIDENT GYNÆCOLOGICAL HOUSE SURGEON for above Hospital. Post vacant 14th September, 1957. 6 months appointment. Recognised for M.R.C.O.G. purposes.

Applications, stating age, qualifications, experience and enclosing copies of up to 3 recent testimonials, to Medical Director of Hospital by 31st August, 1957.

EDINBURGH. ROYAL EDINBURGH HOSPITAL FOR MENTAL AND NERVOUS DISORDERS. Applications are invited for appointment of SENIOR HOUSE OFFICER (resident or non-resident) in this Teaching Hospital with good opportunities of training in psychiatry. Appointment for 1 year from 1st October, 1957.

Applications, stating qualifications, experience, and names of 2 referees, to Physician-Superintendent, Royal Edinburgh Hospital, Morningside-place, Edinburgh, 10, as soon as possible.

EDINBURGH. ROYAL VICTORIA HOSPITAL, Comely BANK, EDINBURGH. RESIDENT HOUSE OFFICER (Male or Female) required for above Hospital on 1st October, 1957. Post offers good experience in the modern management of tuberculosis and includes work in the 20-Bed Unit for tuberculous diabetics. The Hospital is a Teaching Unit linked to the University Department of Tuberculosis and Chest Diseases. The post is recognisable for pre-registration purposes and would also suit anyone studying for higher qualifications.

Applications to be submitted within 2 weeks of appearance of this notice to the Secretary, Boards Office, City Hospital, Greenbank-drive, Edinburgh.

EAST ANGLIAN REGIONAL HOSPITAL BOARD. REGISTRAR in Psychiatry, St. Andrew's Hospital, Thorpe, Norwich (1250 Beds). Full range of modern psychiatric treatments and a number of associated general hospital outpatient clinics. Married or single quarters available. Appointment for 1 year, renewable for second year.

Applications, stating age, experience, and names of 3 referees, to the Board's Senior Administrative Medical Officer, 117, Chesterton-road, Cambridge, by 26th August, 1957. Candidates invited to visit Hospital by direct arrangement with Medical Superintendent.

EPPING. ST. MARGARET'S HOSPITAL. Applications are invited from fully registered medical practitioners for the posts of HOUSE PHYSICIANS (2) at the above Hospital as from 23rd September, 1957. The appointments, which are in general medicine, are for 6 months, including duties at Honey Lane Hospital for part of this time.

Applications, with 2 recent testimonials, to reach the Group Secretary, Epping Group Hospital Management Committee, "Oak Cottage," The Plain, Epping, Essex, by 23rd August, 1957.

EPSOM DISTRICT HOSPITAL, Dorking-road, Epsom, SURREY. RESIDENT ANÆSTHETIST (Senior House Officer grade) required. 12 months appointment.

Applications, stating age, qualifications, and experience, with copies of 2 recent testimonials, should be sent as soon as possible to Group Secretary at above address.

FARNBOROUGH HOSPITAL, Kent. (800 Beds.) Senior HOUSE OFFICER (E.N.T.) required 1st September. Recognised for F.R.C.S. and D.L.O. Valuable experience in all aspects of E.N.T. work.

Apply, stating age, qualifications with dates, experience and naming 3 referees, to Administrative Officer.

GLASGOW ROYAL INFIRMARY AND ASSOCIATED HOSPITALS BOARD OF MANAGEMENT. SENIOR HOUSE OFFICER in General Medicine/Infectious Diseases. Duties at Belvidere Infectious Diseases Hospital in the first instance.

Write, giving 3 names for reference, not later than 31st August, 1957, to the Secretary, Board of Management for Glasgow Royal Infirmary and Associated Hospitals, 135, Buchanan-street, Glasgow, C.1.

GLASGOW ROYAL INFIRMARY. Senior House Officer in General Medicine. Duties at above Infirmary.

Write, giving 3 names for reference, not later than 31st August, 1957, to the Secretary, Board of Management for Glasgow Royal Infirmary and Associated Hospitals, 135, Buchanan-street, Glasgow, C.1.

GLASGOW ROYAL INFIRMARY. Junior House Officers required for the period to 31st January, 1958, in the following specialties :—

Plastic Surgery (1 vacancy).
Orthopædics (2 vacancies).
Ophthalmology (1 vacancy).
Ear, Nose and Throat (1 vacancy).

Apply in writing, giving 2 names for reference, to the Group Medical Superintendent, Glasgow Royal Infirmary, 84, Castle-street, Glasgow, C.1.

GLASGOW, E.3. ROBROYSTON HOSPITAL. Junior HOSPITAL MEDICAL OFFICER required. Resident or non-resident. The work carried out consists mainly of tuberculous pulmonary disease, though substantial units exist for skeletal and for urological tuberculosis. A small unit for acute respiratory disease exists and there are also units for non-tuberculous chest diseases and for geriatrics.

Applications in writing should be forwarded immediately to the Physician-Superintendent.

HALIFAX GENERAL HOSPITAL. Senior House Officer in General Surgery required at above Hospital. Post vacant 1st September.

Applications to the Group Secretary, Halifax Area Hospitals Management Committee, Royal Halifax Infirmary, Halifax.

GRANTHAM AND KESTEVEN GENERAL HOSPITAL. (117 Beds. Recognised for training for F.R.C.S.) SHEFFIELD REGIONAL HOSPITAL BOARD. Whole-time RESIDENT SURGICAL REGISTRAR required 9th September. Appointment for 1 year in first instance.

Apply to Secretary, Sheffield Regional Hospital Board, Old Fulwood-road, Sheffield, by 26th August, 1957, giving age, nationality, qualifications, present and previous appointments with dates, naming 3 referees.

HALIFAX. NORTHOWRAM HALL HOSPITAL. (108 Beds.) SENIOR HOUSE OFFICER in Chest Diseases required. Post vacant 8th September, 1957. Duties include attendance at busy chest clinic at the Royal Halifax Infirmary and non-tuberculosis chest ward work. This post offers excellent facilities for a study of chest diseases and experience is available with bronchoscopies and bronchograms. Salary £819 10s. p.a., with a deduction of £150 p.a. for board-residence, &c.

Applications to be forwarded to the Group Secretary, Royal Halifax Infirmary, Halifax.

HALIFAX. ROYAL HALIFAX INFIRMARY. House PHYSICIAN required in General Medicine. Post now vacant.

Apply to Group Secretary, Royal Halifax Infirmary, Halifax.

HASLEMERE AND DISTRICT HOSPITAL. Guildford GROUP HOSPITAL MANAGEMENT COMMITTEE. Applications are invited for the appointment of Locum RESIDENT SENIOR HOUSE OFFICER for the period 7th–13th September, 1957. Mainly surgical but with charge of 12 medical beds. Busy General Hospital with easy access to London. General and emergency surgery, orthopædic, E.N.T., gynæcological, children and casualty work.

Applications to Hospital Secretary, Haslemere and District Hospital, Haslemere, Surrey.

HASTINGS HOSPITAL MANAGEMENT COMMITTEE. Locum RESIDENT MEDICAL OFFICER (general medicine) required for whole-time duties for 4 weeks commencing 7th September, 1957. Remuneration £19 5s. per week. Non-resident.

Apply, giving details of qualifications and experience, to Group Secretary, Hastings Hospital Management Committee, 11, Holmesdale-gardens, Hastings.

HASTINGS AND ST. LEONARDS-ON-SEA. BUCHANAN HOSPITAL. (94 Beds.) HOUSE SURGEON required for 28 gynæcological beds in Hospital in course of being changed into unit for obstetric and gynæcological patients only. Post is vacant 8th September and recognised for M.R.C.O.G. Candidates for Pre-registration Service (surgery) can be considered.

Apply, giving names and addresses of 3 referees, to Hospital Administrator.

HASTINGS. ROYAL EAST SUSSEX HOSPITAL. (150 Beds.) 2 HOUSE SURGEONS (pre-registration posts). 1 for general surgery and E.N.T., required early September. 1 for general surgery and urology, post vacant 7th October, 1957.

Apply, with copies of testimonials, to the Hospital Administrator.

HEREFORD. GENERAL HOSPITAL. (154 Beds.) HOUSE OFFICER (general surgery) required, pre-registration post. Hospital recognised by R.C.S. Duties include care of general surgical beds and in addition for 3 months of orthopædic beds and for 3 months of E.N.T. beds.

Applications, with copies of 2 testimonials, to be sent to the Group Secretary, Victoria House, Eign-street, Hereford.

HEREFORDSHIRE GROUP OF HOSPITALS. Registrar in General Medicine. Duties mainly at County Hospital (339 Beds) and General Hospital (154 Beds). Resident or non-resident.

Application forms from Group Secretary, Victoria House, Eign-street, Hereford, to be returned by 30th August, 1957. Candidates may visit Group Hospitals.

HILLINGDON HOSPITAL, Uxbridge, Middlesex. (621 Beds.) PÆDIATRIC HOUSE PHYSICIAN. Duties include experience in general children's medical ward, Neo-natal Unit and pædiatric outpatient clinics. Post vacant beginning October. Appointment recognised for D.C.H. Applications accepted from registered and pre-registered practitioners.

Apply, stating age, qualifications, nationality and experience, with copies of not more than 3 recent testimonials, to Medical Director by 27th August.

HILLINGDON HOSPITAL, Uxbridge, Middlesex. (621 Beds.) HOUSE PHYSICIANS. Appointments recognised for M.D. (Lond.) Branch I and for pre-registration House Officers. Posts vacant middle September.

Apply, stating age, qualifications, nationality and experience, with copies of not more than 3 recent testimonials, to Medical Director by 27th August.

HITCHIN, HERTFORDSHIRE. LISTER HOSPITAL. CASUALTY OFFICER (resident) now required, for duty with Accident Service and as Orthopædic House Surgeon. Recognised as pre-registration post.

Applications, stating age, nationality, qualifications and experience, together with copies of 3 recent testimonials, to Medical Administrator, Lister Hospital as soon as possible.

HUDDERSFIELD ROYAL INFIRMARY. (285 Beds.) HUDDERSFIELD HOSPITAL MANAGEMENT COMMITTEE. HOUSE SURGEON required to commence duty immediately. The post is recognised as a pre-registration appointment and for the F.R.C.S. Salary in accordance with national scale.

Applications, together with copies of 3 recent testimonials, to be addressed to the undersigned as soon as possible.

H. J. JOHNSON, Secretary to the Management Committee.
The Royal Infirmary, Huddersfield.

HULL. KINGSTON GENERAL HOSPITAL. (419 Beds.) HULL A GROUP HOSPITAL MANAGEMENT COMMITTEE. HOUSE SURGEON (pre-registration post), resident, and tenable for 6 months. This post includes gynæcology and general surgery.

Applications, with 2 recent testimonials, to the Hospital Secretary.

HULL. VICTORIA HOSPITAL FOR SICK CHILDREN, Park-street. Locum CASUALTY OFFICER (Senior House Officer grade) required for the month of September, 1957.

Applications should be sent to the Hospital Secretary.

IPSWICH AND EAST SUFFOLK HOSPITAL. Anglesea ROAD WING. (356 Beds.) Applications are invited for the post of HOUSE SURGEON to the E.N.T. and Ophthalmic Departments. The post is recognised for pre-registration and for the D.L.O. examination.

Applications, giving full particulars and copies of recent testimonials, to Hospital Secretary.

IPSWICH AND EAST SUFFOLK HOSPITAL. Anglesea ROAD WING. (356 Beds.) Applications are invited for the post of HOUSE SURGEON to the Fracture and Orthopædic Department. Approved pre-registration post.

Applications, with copies of recent testimonials, to the Hospital Secretary.

ISLEWORTH. SOUTH MIDDLESEX HOSPITAL. SENIOR HOUSE OFFICER for Ophthalmic Unit (29 Beds) vacant 27th September. Post recognised for F.R.C.S. and D.O. qualifications.

Applications, stating age, nationality, qualifications, and experience, with copies of up to 3 recent testimonials, to Group Secretary, South West Middlesex Hospital Management Committee, West Middlesex Hospital, Isleworth, by 28th August, 1957.

LANCASTER. BEAUMONT HOSPITAL, Slyne-road. SENIOR HOUSE OFFICER (infectious diseases). Hospital recognised for D.C.H. and contains a Pædiatric Unit, Dermatological Unit, Infectious Diseases Department and Pulmonary Tuberculosis Unit.

Applications, together with names of 2 referees, to Group Secretary, Royal Lancaster Infirmary, Lancaster.

LEEDS. THE UNITED LEEDS HOSPITALS. The GENERAL INFIRMARY AT LEEDS. RESIDENT SURGICAL OFFICER of Registrar status required for 1 year in the first instance. Terms and conditions of service of hospital medical staff apply.

Applications, stating age, qualifications, previous posts with dates, and 3 names for reference, should be sent to the Sub-Dean, School of Medicine, Leeds, 1, not later than 22nd August, 1957.

LEICESTER. GENERAL HOSPITAL. (445 Beds. Post recognised for F.R.C.S.) SHEFFIELD REGIONAL HOSPITAL BOARD. Whole-time RESIDENT SURGICAL REGISTRAR required 1st October. Appointment for 1 year in first instance.

Apply to Secretary, Sheffield Regional Hospital Board, Old Fulwood-road, Sheffield, by 26th August, 1957, giving age, nationality, qualifications, present and previous appointments with dates, naming 3 referees.

LEICESTER ROYAL INFIRMARY. (492 Beds. Recognised for the F.F.A.R.C.S.) SHEFFIELD REGIONAL HOSPITAL BOARD. Whole-time RESIDENT REGISTRAR (anæsthetics) required 29th September. Appointment for 1 year in first instance.

Apply to Secretary, Sheffield Regional Hospital Board, Old Fulwood-road, Sheffield, by 26th August, 1957, giving age, nationality, qualifications, present and previous appointments with dates, naming 3 referees.

LEICESTER. TOWERS MENTAL HOSPITAL. (1168 Beds.) Applications are invited for the whole-time post of JUNIOR HOSPITAL MEDICAL OFFICER. Salary £852 10s.–£55–£1182 10s. There is ample opportunity for experience in all branches of psychiatry, including outpatient work and the Hospital is recognised for D.P.M. experience. Facilities for postgraduate training exist at Sheffield University. Resident accommodation is not available. Candidates must have completed their service with H.M. Forces.

Applications, giving age, nationality, and full details with the names of 2 referees, to be sent to the Medical Superintendent as soon as possible.

LICHFIELD. ST. MATTHEW'S HOSPITAL, Burntwood, LICHFIELD, STAFFS. (1330 mental beds.) BURTON-ON-TRENT HOSPITAL MANAGEMENT COMMITTEE. JUNIOR HOSPITAL MEDICAL OFFICER (psychiatry) required. Resident accommodation available. Facilities for taking a D.P.M. Course at Birmingham University.

Applications, with 2 references, to the Medical Superintendent.

LIVERPOOL. THE UNITED LIVERPOOL HOSPITALS. Applications are invited for a post of REGISTRAR in Pathology for duties initially at The Women's Hospital, Liverpool, for the period 1st September, 1957 (or as soon thereafter as possible), to 30th September, 1958. Annual reappointment until completion of the normal period of training will be considered without need for further application.

Apply by 28th August on form obtainable from the Secretary, The United Liverpool Hospitals, 80, Rodney-street, Liverpool, 1.

LOUTH. COUNTY HOSPITAL. (215 Beds.) Sheffield REGIONAL HOSPITAL BOARD. Whole-time RESIDENT or NON-RESIDENT REGISTRAR (orthopædics and casualty) required. The appointment may include some duties in general surgery. Appointment for 1 year in first instance.

Apply to Secretary, Sheffield Regional Hospital Board, Old Fulwood-road, Sheffield, by 26th August, 1957, giving age, nationality, qualifications, present and previous appointments with dates, naming 3 referees.

MIDDLESBROUGH. GENERAL HOSPITAL, Ayresome Green-lane, MIDDLESBROUGH. TEES-SIDE HOSPITAL MANAGEMENT COMMITTEE. Applications are invited for the appointment of a HOUSE PHYSICIAN (pædiatrics) at the above Hospital. The Pædiatric Unit is a very active one of 60 Beds and Cots for acute cases and a busy Outpatient Department. The post is recognised for Pre-registration Service and for the D.C.H. examination.

Applications, stating age, qualifications, experience and giving names of 2 referees, should be addressed to the Hospital Secretary.

LINCOLN COUNTY HOSPITAL. (200 Beds.) Applications are invited from pre-registration candidates for appointments as HOUSE SURGEONS for 6 months to be followed if satisfactory by appointments as House Physicians for a further 6 months.

Full particulars should be sent to—
R. W. HOWICK, Group Secretary.

MANCHESTER. DUCHESS OF YORK HOSPITAL FOR BABIES, MANCHESTER, 19, AND WYTHENSHAWE HOSPITAL. SOUTH MANCHESTER HOSPITAL MANAGEMENT COMMITTEE. Applications are invited for the post of SENIOR HOUSE OFFICER (pædiatrics) vacant 1st October. A joint post of not less than 3 months and preferably 6 months at each Hospital is recognised as training for the D.C.H.

Applications, with full details and the names of 2 referees, to the Group Secretary, Withington Hospital, Manchester, 20.

MANCHESTER (near). PRESTWICH (MENTAL) HOSPITAL. JUNIOR HOSPITAL MEDICAL OFFICER required at above Hospital. Single quarters available, or may be non-resident. All modern treatments practised and study facilities granted.

Applications, giving full details and names and addresses of 2 referees, should be sent immediately to Medical Superintendent, Prestwich Hospital, Prestwich, near Manchester.

MANCHESTER REGIONAL HOSPITAL BOARD. SALFORD HOSPITAL MANAGEMENT COMMITTEE. REGISTRAR in Neurosurgery required with duties at Salford Royal Hospital and the Royal Manchester Children's Hospital. Resident or non-resident.

Applications, with names of 2 referees, to Group Secretary, Salford Royal Hospital, Salford, 3, immediately.

MANCHESTER REGIONAL HOSPITAL BOARD. BLACKBURN ROYAL INFIRMARY. REGISTRAR (medicine) required early September, 1957. Resident post. Duties at Royal Infirmary Blackburn (262 acute beds), as arranged by Consultant-Physician.

Application forms from Group Secretary, Hospital Management Committee Office, Royal Infirmary, Blackburn, Lancs.

MANCHESTER REGIONAL HOSPITAL BOARD. BURY AND ROSSENDALE, AND ROCHDALE AND DISTRICT HOSPITAL MANAGEMENT COMMITTEES. Applications are invited for the post of REGISTRAR in Pædiatrics which is now vacant. The successful applicant, who may be either resident or non-resident, will have duties in the Neo-natal Departments and Children's Units at hospitals in the above Groups, which are recognised for the D.C.H. The person appointed to the post will supervise the work of Senior House Officers in both Groups and assist the Consultant Pædiatrician.

Apply, stating full details of experience and qualifications, together with names of 2 referees, to—
H. WILKINSON, Group Secretary.

Bury General Hospital, Bury, Lancs.

MANCHESTER REGIONAL HOSPITAL BOARD. BIRCH HILL HOSPITAL. REGISTRAR in Obstetrics and Gynæcology required 1st October. Recognised for D.Obst.R.C.O.G. House available, unfurnished or partly furnished, at a moderate rental. Interviews to be held 2nd September.

Apply at once to Group Secretary, Central Offices, Birch Hill Hospital, Rochdale, Lancs.

MANCHESTER REGIONAL HOSPITAL BOARD. ROCHDALE INFIRMARY. (109 surgical beds.) RESIDENT SURGICAL OFFICER (Registrar grade) required for this busy surgical hospital which has a large Outpatients Department. Recognised for F.R.C.S. Post vacant 1st September, 1957.

Apply at once, with details of experience and qualifications and names of 3 referees, to Group Secretary, Central Offices, Birch Hill Hospital, Rochdale.

MEXBOROUGH. MONTAGU HOSPITAL. (168 Beds. Recognised for Final Fellowship examination.) SHEFFIELD REGIONAL HOSPITAL BOARD. Whole-time RESIDENT SURGICAL REGISTRAR required on 18th October. Appointment for 1 year in first instance.

Apply to Secretary, Sheffield Regional Hospital Board, Old Fulwood-road, Sheffield, by 26th August, 1957, giving age, nationality, qualifications, present and previous appointments with dates, naming 3 referees.

NEWPORT, MONMOUTHSHIRE. ROYAL GWENT HOSPITAL. (260 Beds. 10 Residents. Recognised F.R.C.S.) SENIOR HOUSE OFFICER required for Casualty Department which is under the full-time charge of a Senior Hospital Medical Officer and there are also 2 Senior House Officers. The Department has recently been rebuilt and re-equipped, and all medical and surgical emergency admissions pass through it. Tenable for 6 or 12 months at candidate's option. Excellent experience.

Write, quoting 2 referees, to T. A. JONES, Group Secretary, 64, Cardiff-road, Newport, Mon.

NEWCASTLE. THE UNITED NEWCASTLE UPON TYNE HOSPITALS. Applications are invited for the whole-time non-resident appointment of SENIOR REGISTRAR OPHTHALMOLOGIST, in the first year tenable at the Royal Victoria Infirmary which is the teaching hospital of the University of Durham. The successful candidate will have opportunity for clinical experience in outpatient and inpatient work under the direction of the Head of the Department and will be responsible for clinical emergency duty as required. Applicants must possess the D.O.M.S. or higher qualification. The appointment is for 1 year in the first instance, and may be renewed to a maximum of 4 years. In any reappointment the successful candidate may be required to undertake duty in a hospital under the Newcastle Regional Hospital Board. The appointment will be subject to the terms and conditions of service of hospital medical staff in the National Health Service.

Applications, giving full details and the names and addresses of 3 referees, should be sent to the undersigned within 2 weeks of the appearance of this advertisement.

A. W. SANDERSON, House Governor and Secretary.
Royal Victoria Infirmary, Newcastle upon Tyne.

NEWCASTLE. THE UNITED NEWCASTLE UPON TYNE HOSPITALS. Applications are invited for the whole-time resident appointment of SENIOR HOUSE OFFICER in the Babies' Hospital. The appointment will be for 1 year and will be subject to the terms and conditions of service of hospital medical staff in the National Health Service. The salary will be at the rate of £819 10s. p.a., subject to the appropriate deductions.

Applications, giving full particulars and the names and addresses of 3 referees, should be sent to the undersigned within 2 weeks of the appearance of this advertisement.

A. W. SANDERSON, House Governor and Secretary.
Royal Victoria Infirmary, Newcastle upon Tyne.

NEWCASTLE. THE UNITED NEWCASTLE UPON TYNE HOSPITALS. Applications are invited for the whole-time non-resident appointment of REGISTRAR in the Department of Psychological Medicine at the Royal Victoria Infirmary. The successful candidate will work under the direction of the Head of the Department and will be expected to undertake some teaching in his subject. The appointment is for 1 year in the first instance, and will be subject to Ministry of Health terms and conditions of service for hospital medical staff in the National Health Service.

Applications, giving full details and the names and addresses of 3 referees, should be sent to the undersigned within 2 weeks of the appearance of this advertisement.

A. W. SANDERSON, House Governor and Secretary.
Royal Victoria Infirmary, Newcastle upon Tyne.

NEWCASTLE REGIONAL HOSPITAL BOARD. Senior REGISTRAR in Neuro-radiology, whole-time, for Newcastle General Hospital (848 Beds), where there is a Regional Neurosurgical Unit, together with a newly developed Neuro-radiological Department.

Applications, with names and addresses of 3 referees, to Senior Administrative Medical Officer, Regional Hospital Board, Benfield-road, Newcastle upon Tyne, 6, within 21 days.

NEWCASTLE REGIONAL HOSPITAL BOARD. Senior REGISTRAR OPHTHALMOLOGIST (whole-time), Newcastle upon Tyne Group of Hospitals—main hospitals Newcastle General (848 Beds); Walker Gate Hospital (309 Beds—42 ophthalmic); Walker Accident (21 ophthalmic beds). Candidates should hold a D.O. or D.O.M.S.

Applications, with names and addresses of 3 referees, to Senior Administrative Medical Officer, Regional Hospital Board, Benfield-road, Newcastle upon Tyne, 6, within 14 days.

NEWCASTLE REGIONAL HOSPITAL BOARD. REGISTRAR OPHTHALMOLOGIST (whole-time), Newcastle upon Tyne Group of Hospitals—main hospitals: Newcastle General (848 Beds); Walker Gate Hospital (309 Beds—42 ophthalmic); Walker Accident (21 ophthalmic beds).

Applications, with names and addresses of 3 referees, to Senior Administrative Medical Officer, Regional Hospital Board, Benfield-road, Newcastle upon Tyne, 6, within 14 days.

NEWCASTLE REGIONAL HOSPITAL BOARD. REGISTRAR PATHOLOGIST (whole-time), Sunderland Group of hospitals—main hospital: Sunderland Royal Infirmary (312 Beds). Post available from 14th September, 1957. Married or single accommodation available.

Applications, with names and addresses of 3 referees, to Senior Administrative Medical Officer, Regional Hospital Board, Benfield-road, Newcastle upon Tyne, 6, within 14 days.

NEWTON ABBOT HOSPITAL, S. Devon. Senior House OFFICER (medicine), Male or Female, required approximately 1st October, 1957. Duties divided equally between 20 acute medical beds in General Section and 140 geriatric beds. This Officer is also required to stand in when Senior House Surgeon otherwise engaged. Married quarters available.

Applications, stating qualifications, nationality, age, with copy testimonials, to be sent to the Group Secretary, Torquay District Hospital Management Committee, Torbay Hospital, Torquay, S. Devon.

NORTH MANCHESTER HOSPITAL MANAGEMENT COMMITTEE. Applications are invited for the post of REGISTRAR in Anæsthetics in the North Manchester Group and Beoth Hall Hospital. Resident or non-resident. Recognised for D.A. and F.F.A.R.C.S.

Applications, with names of 2 referees, by 30th August, 1957, to Group Secretary, Crumpsall Hospital, Manchester, 8.

NORTHWOOD, MIDDLESEX. MOUNT VERNON HOSPITAL. NORTH WEST METROPOLITAN REGIONAL HOSPITAL BOARD. ANÆSTHETIC REGISTRAR (resident) required for 1 year in first instance. This post is recognised for F.F.A.R.C.S. examination.

Application forms obtainable from, and returnable to, the Group Secretary, Harefield and Northwood Group Hospital Management Committee, Mount Vernon Hospital, Northwood, Middlesex, by 31st August, 1957.

NORTHWOOD, MIDDLESEX. MOUNT VERNON HOSPITAL. (551 Beds.) NORTH WEST METROPOLITAN REGIONAL HOSPITAL BOARD. REGISTRAR required in the X-ray Diagnostic Department at above Hospital for 1 year in first instance.

Application forms obtainable from, and returnable to, the Group Secretary, Harefield and Northwood Group Hospital Management Committee, Mount Vernon Hospital, Northwood, Middx, by 27th August, 1957. Hospital may be visited by direct appointment.

NUNEATON. GEORGE ELIOT HOSPITAL. House SURGEON (general surgery). Recognised pre-registration and F.R.C.S. Resident.

Applications to Hospital Secretary.

NOTTINGHAM GENERAL HOSPITAL. A Senior HOUSE OFFICER (orthopædic and fracture) required 30th September. Post offers exceptional experience in traumatic surgery.

Applications, stating age, qualifications, experience, nationality together with copies of testimonials, to be sent to Group Secretary.

NOTTINGHAM GENERAL HOSPITAL. (428 Beds, 51 E.N.T. beds. Post recognised for the F.R.C.S.) SHEFFIELD REGIONAL HOSPITAL BOARD. Whole-time RESIDENT or NON-RESIDENT REGISTRAR in E.N.T. Surgery. Appointment for 1 year in first instance.

Apply to Secretary, Sheffield Regional Hospital Board, Old Fulwood-road, Sheffield, by 26th August, 1957, giving age, nationality, qualifications, present and previous appointments with dates, naming 3 referees.

NOTTINGHAM CHILDREN'S HOSPITAL. (136 Beds. Recognised for the D.C.H.) Applications are invited for the post of SENIOR HOUSE OFFICER (surgical) which will be vacant mid-September. The post is tenable for 6 months or a year by agreement.

Applications, with the copies of 2 testimonials, should be sent to the Secretary, Nottingham Children's Hospital, Chestnut-grove, Nottingham.

NOTTINGHAM CHILDREN'S HOSPITAL. (136 Beds. Recognised for the D.C.H.) Applications are invited for the post of SENIOR HOUSE OFFICER (medical), vacant early September. The post is tenable for 6 months or a year by agreement.

Applications, with copies of 2 testimonials, should be sent to the Secretary, Nottingham Children's Hospital, Chestnut-grove, Nottingham.

NOTTINGHAM. CITY HOSPITAL. (811 Beds.) Applications are invited for the post of HOUSE OFFICER (obstetrics and gynæcology), recognised for pre-registration purposes which will be graded Senior House Officer or House Officer in accordance with experience. Recognised for the M.R.C.O.G. and D.Obst.R.C.O.G. Post vacant on 6th October, 1957.

Applications, stating age, nationality, qualifications, and experience, together with copies of not more than 3 testimonials, to be sent to the Hospital Secretary, City Hospital, Hucknall-road, Nottingham.

OXFORD. NUFFIELD ORTHOPÆDIC CENTRE, HEADINGTON, OXFORD. Applications are invited from suitably qualified persons for a SENIOR HOUSE OFFICER grade appointment from 1st October, 1957.

Applications, with names of referees, to be submitted to the Secretary by 31st August.

OXFORD REGIONAL HOSPITAL BOARD. Registrar in Ophthalmology (resident or non-resident) to Northampton General Hospital. A new department of 32 beds is being opened.

Applications, on forms obtainable from the Secretary, Registrar Committee, 43, Banbury-road, Oxford, should reach him by 31st August, 1957.

OXFORD REGIONAL HOSPITAL BOARD. Registrar in Orthopædic and Accident Surgery to the Reading Group of hospitals. (Recognised for the F.R.C.S.) The appointment will be for 1 year and eligible for extension to 2 years. Vacant 1st October.

Applications, on forms obtainable from the Secretary, Registrar Committee, 43, Banbury-road, Oxford, to reach him by 31st August.

OXFORD REGIONAL HOSPITAL BOARD. Senior REGISTRAR in Obstetrics and Gynæcology to the Combined Reading Hospitals (100 Beds). Applicants should preferably hold the M.R.C.O.G.

Applications, on forms obtainable from the Secretary, Registrar Committee (from whom further details may be obtained), 43, Banbury-road, Oxford, should reach him by 31st August.

OXFORD. UNITED OXFORD HOSPITALS: OXFORD REGIONAL HOSPITAL BOARD. FIRST ASSISTANT (Senior Registrar) to the Accident Service in the United Oxford Hospitals, interchangeable with an orthopædic post in the Nuffield Orthopædic Centre, Oxford. The period of tenure will be approximately equally divided between the 2 posts, and the successful candidate may be required to start in either. Candidates should be Fellows of 1 of the Royal Colleges of Surgeons. Experience in both branches of orthopædics is essential.

Applications, on forms obtainable from the Secretary, Joint Committee for Senior Registrars, 43, Banbury-road, Oxford, should reach him by 31st August.

PORTSMOUTH GROUP HOSPITAL MANAGEMENT COMMITTEE. QUEEN ALEXANDRA HOSPITAL. (78 medical beds.) HOUSE PHYSICIANS (pre-registration), 1 vacant now, 1 vacant 15th September.

Applications, stating age, experience and qualifications, together with the names of 2 referees, should be forwarded as soon as possible to E. H. HURST.

Saint Mary's Hospital, Milton-road, Portsmouth.

ROMFORD, ESSEX. VICTORIA HOSPITAL. (99 Beds.) RESIDENT HOUSE SURGEON (Male) required immediately. (Not pre-registration appointment.)

Applications should be forwarded to the Secretary, Romford Group Hospital Management Committee, Oldchurch Hospital, Romford.

READING AND DISTRICT HOSPITAL MANAGEMENT COMMITTEE. Applications are invited for the post of RESIDENT SENIOR HOUSE OFFICER (area Accident and Orthopædic Department), vacant immediately. Recognised for F.R.C.S. Duties including work in area Casualty Department at Battle Hospital, Reading (300 Beds). Person appointed will work with Registrar and House Officers.

Apply, stating nationality, present post, and qualifications with dates, together with names of 2 referees, to Group Secretary, 3, Craven-road, Reading.

READING. BATTLE HOSPITAL. (391 Beds.) Applications are invited from registered medical practitioners for the post of RESIDENT JUNIOR HOUSE SURGEON in the Accident and Orthopædic Department. Post vacant immediately. F.R.C.S. recognised. Also casualty duties.

Apply, stating age, qualifications with dates, nationality, present post, with 1 copy of recent testimonial, to Hospital Secretary.

READING AREA DEPARTMENT OF MEDICINE. Applications are invited from registered and provisionally registered medical practitioners for 2 posts as RESIDENT HOUSE PHYSICIAN vacant 1st September, 1957, for a period of 6 months. Successful candidates will be required to carry out duties at the following Reading Hospitals: Royal Berkshire Hospital (398 Beds), Battle (374 Beds) and Prospect Park (104 Beds).

Write immediately, stating age, qualifications with dates, nationality, present post, with copies of 2 recent testimonials, to Secretary, Royal Berkshire Hospital, Reading.

ROCHFORD, ESSEX. GENERAL HOSPITAL. (622 Beds.) HOUSE PHYSICIAN (pre-registration) required, vacant 14th September, 1957.

Applications, &c. (1 testimonial only necessary for pre-registration applicant seeking first appointment), to be sent to the undersigned by 26th August, 1957. J. C. FIELD, Secretary.

ROCHFORD, ESSEX. GENERAL HOSPITAL. (622 Beds.) Required, SENIOR HOUSE OFFICER (medical). Post Resident and tenable for 1 year, commencing 3rd September, 1957, for duties in modern General Hospital.

Applications, &c., to reach the undersigned by 21st August, 1957. J. C. FIELD, Secretary.

SALISBURY. PLASTIC AND ORAL SURGERY CENTRE, ODSTOCK HOSPITAL, SALISBURY. RESEARCH ASSISTANT required for work on the application of physical methods to clinical problems with special reference to peripheral circulation studies. Initial training in radio-isotope techniques can be provided. Appointment is for 1 year in the first instance. Salary according to qualifications and experience.

Applications to Group Secretary, Odstock Hospital, Salisbury, by 9th September.

SCOTLAND. EASTERN REGIONAL HOSPITAL BOARD. DUNDEE ROYAL INFIRMARY. E.N.T. Surgery. Applications are invited for the post of Locum REGISTRAR in E.N.T. Surgery at Dundee Royal Infirmary (534 Beds), for 3 months from 1st October, 1957. Previous experience in the specialty essential. Salary and conditions of service in accordance with national agreement.

Applications, stating qualifications and experience and naming 2 referees, should be lodged with the Secretary to the Board, 430, Blackness-road, Dundee, not later than 31st August, 1957.

SCOTLAND. EASTERN REGIONAL HOSPITAL BOARD. General Surgery. DUNDEE TEACHING HOSPITALS. Applications are invited for a post as REGISTRAR attached to the Dundee Teaching Hospitals (Dundee Royal Infirmary, 534 Beds, and Maryfield Hospital 370 Beds). Applicants should have had previous experience in general surgery and have passed at least a Primary Fellowship examination. Salary and conditions in accordance with national agreement.

Further particulars and forms of application may be obtained from the Secretary to the Board, 430, Blackness-road, Dundee, with whom applications must be lodged not later than 31st August, 1957.

SCOTLAND. EASTERN REGIONAL HOSPITAL BOARD. DUNDEE AREA. Thoracic (and Cardiac) Surgery. Applications are invited for the appointment of REGISTRAR in Surgery for duty in the Regional Thoracic Surgical Centre at Ashludie Hospital, Monifieth, by Dundee (222 Beds—60 for thoracic surgery), and in the Cardiovascular Department of the Professorial Surgical Unit at Dundee Royal Infirmary (the principal general teaching hospital associated with the University of St. Andrews—534 Beds). Previous experience in thoracic surgery and in general chest medicine an advantage. Salary and conditions of service in accordance with national agreement.

Further particulars and forms of application from the Secretary to the Board, 430, Blackness-road, Dundee, with whom applications must be lodged not later than 31st August, 1957.

SCOTLAND. SOUTH-EASTERN REGIONAL HOSPITAL BOARD. Applications are invited for the post of REGISTRAR to the Royal Edinburgh Hospital for Mental and Nervous Disorders. During tenure of post opportunities for study and interchange of duty and training at other centres in the Region may be available under joint training scheme of South-Eastern Regional Hospital Board and Department of Psychological Medicine of the University of Edinburgh. Single accommodation available. The Hospital may be visited by arrangement with the Physician-Superintendent.

Apply, giving particulars of age, qualifications and previous experience and the names of 2 referees, to the Secretary, 11, Drumsheugh-gardens, Edinburgh, 3, within 14 days.

SCOTLAND. NORTH-EASTERN REGIONAL HOSPITAL BOARD. Applications are invited for the post of REGISTRAR or SENIOR REGISTRAR in Dermatology at the Aberdeen Royal Infirmary. The appointment will be filled in either of these grades according to the experience and qualifications of the applicant. Opportunity will be given for further study and training in general medical subjects by arrangement with the Department of Medicine.

Applications, giving the names of 2 referees, should be submitted by 6th September, 1957, to the Secretary, North-Eastern Regional Hospital Board, Scotland, 1, Albyn-place, Aberdeen, from whom further particulars may be obtained.

SCOTLAND. NORTHERN REGIONAL HOSPITAL BOARD invites applications for the post of Whole-time NON-RESIDENT JUNIOR HOSPITAL MEDICAL OFFICER at Inverness. The post provides experience in general practice as Locum Tenens as well as hospital work in selected departments. Tenure of appointment is 1 year.

A note of further particulars and an application form are obtainable from the undersigned, with whom applications should be lodged by 7th September, 1957.

A. M. FRASER, M.D.,
Secretary and Administrative Medical Officer.
Office of the Northern Regional Hospital Board,
Raigmore, Inverness.

SCOTLAND. NORTHERN REGIONAL HOSPITAL BOARD. Applications are invited for the whole-time post of REGISTRAR in Anæsthetics. Duties mainly at the Royal Northern Infirmary, Inverness, and Raigmore Hospital, Inverness.

Forms of application and further particulars may be obtained from the undersigned, with whom applications should be lodged by 9th September, 1957. A. M. FRASER, M.D.,
Secretary and Administrative Medical Officer.
Office of the Northern Regional Hospital Board,
Raigmore, Inverness.

SCOTLAND. WESTERN REGIONAL HOSPITAL BOARD. Applications are invited for the appointment, which will be for 1 year in the first instance with possibility of renewal, of TRAINEE MEDICAL ADMINISTRATOR on the staff of the Western Regional Hospital Board. The person appointed will be seconded for duties at the hospitals administered by the Board of Management for Glasgow South-Western Hospitals but he will also be given the opportunity of obtaining some experience in medical administration at Regional level. Salary in the first year £1100 p.a.

Applications (16 copies), stating date of birth, qualifications, experience, present appointment, and the names of 3 referees, to reach the Secretary, Western Regional Hospital Board, 64, West Regent-street, Glasgow, C.2, not later than 30 days after the publication of this advertisement.

SHEFFIELD. CITY GENERAL HOSPITAL. (652 Beds Recognised for Final Fellowship examination.) SHEFFIELD REGIONAL HOSPITAL BOARD. Whole-time NON-RESIDENT SURGICAL REGISTRAR required on 11th October. The successful candidate to reside at the Hospital when "on call." This is a large general hospital with teaching affiliations. Appointment for 1 year in first instance.

Apply to Secretary, Sheffield Regional Hospital Board, Old Fulwood-road, Sheffield, by 26th August, 1957, giving age, nationality, qualifications, present and previous appointments with dates, naming 3 referees.

SHEFFIELD. NETHER EDGE HOSPITAL. Applications are invited for the resident post of SENIOR HOUSE OFFICER. Main duties will be in connection with the Maternity Unit but will also be required to assist in the wards for long-stay medical cases. Small flat available on rental.

Apply, giving full details of age, qualifications, present and previous appointments with dates, and the names of 2 persons for reference, to the Group Secretary, Nether Edge Hospital, Sheffield, 11.

SHREWSBURY. ROYAL SALOP INFIRMARY AND COPTHORNE HOSPITAL. (500 Beds.) RESIDENT ANÆSTHETIST (Senior House Officer). Post recognised for F.F.A.R.C.S. Registrar also employed. Vacant mid-September.

Applications and copy testimonials to Group Secretary, Shrewsbury Hospital Group, Royal Salop Infirmary, Shrewsbury.

SLOUGH, BUCKINGHAMSHIRE. UPTON HOSPITAL. Locum SENIOR SURGICAL REGISTRAR required 2nd–15th September.

Applications, with names of 2 referees, to Secretary.

SOUTHEND-ON-SEA GENERAL HOSPITAL. Locum MEDICAL REGISTRAR (resident or non-resident) required for 9th–28th September, 1957, inclusive.

Applications, giving details of age, qualifications, testimonials, &c., to be sent to the undersigned as soon as possible.
J. C. FIELD, Secretary.

SOUTH WEST METROPOLITAN REGIONAL HOSPITAL BOARD. Psychiatric Registrars Training Scheme. Applications are invited for the appointment of REGISTRAR, with effect from 1st January, 1958, for 6 months periods at the Hospitals Knowle, Fareham; Coldeast, Sarisbury, near Southampton; St. James' Portsmouth; and Moorgreen, Southampton, in succession. These appointments afford wide experience in the treatment of all forms of nervous and mental disorder, including cases admitted to the observation ward at Moorgreen Hospital, and in mental deficiency. In addition there are special opportunities for experience in the Department of Child Psychiatry (inpatients and outpatients), in electro-encephalography and in neurology at St. James' Hospital. Salary, &c., in accordance with the agreed terms and conditions of service for hospital medical staff. For residents the appropriate charges are made for full residential amenities. Candidates may visit the hospitals by appointment with the Physician-Superintendent.

Application forms may be obtained from the Group Secretary, Knowle Hospital, Fareham, Hants, to whom 5 copies should be sent within 2 weeks of the appearance of this advertisement.

SOUTHAMPTON CHEST HOSPITAL. (252 Beds.) SENIOR HOUSE OFFICER required, to be responsible for Infectious Diseases Unit. The duties are such as to suit a candidate reading for higher examinations. The Unit is sited at a Hospital possessing up-to-date Tuberculosis and Thoracic Surgical Units, whilst the Southampton Group of hospitals as a whole affords excellent opportunities for study and experience in all branches of medicine.

Applications, together with copies of recent testimonials, should be forwarded as soon as possible to the Group Secretary, Southampton Group Hospital Management Committee, Bullar-street, Southampton.

SOUTHAMPTON. ROYAL SOUTH HANTS HOSPITAL. (274 Beds.) RESIDENT HOUSE SURGEON required beginning of October. Pre-registration candidates eligible.

Applications, with copies of recent testimonials, should be forwarded to Group Secretary, Southampton Group Hospital Management Committee, Bullar-street, Southampton.

SOUTHAMPTON. ROYAL SOUTH HANTS HOSPITAL. (274 Beds.) RESIDENT HOUSE PHYSICIAN required mid-September. Pre-registration candidates eligible.

Applications, with copies of testimonials, should be forwarded to Group Secretary, Southampton Group Hospital Management Committee, Bullar-street, Southampton, as soon as possible.

SOUTHAMPTON. ROYAL SOUTH HANTS HOSPITAL. (274 Beds.) ORTHOPÆDIC HOUSE SURGEON (post recognised for Pre-registration Service and tenable for 6 months) and SENIOR HOUSE OFFICER (orthopædic). The Hospital is the centre to which all trauma from a large industrial town and port is directed thus providing excellent experience in the treatment of traumatic conditions; patients with orthopædic conditions are also drawn from a wide area.

Applications, with copies of testimonials, should be sent as soon as possible to the Group Secretary, Southampton Group Hospital Management Committee, Bullar-street, Southampton.

SOUTHAMPTON GROUP OF HOSPITALS. South West METROPOLITAN REGIONAL HOSPITAL BOARD. Applications are invited for the post of Whole-time ANÆSTHETIC REGISTRAR to the above Group, for work in the General and Special Units. Special facilities for working for Primary or Final F.F.A.R.C.S.

Forms of application may be obtained from the undersigned and should be returned by Wednesday, 28th August, 1957. Applicants should state in their initial application if they wish to be considered on a locum basis from 1st September, 1957, until the permanent appointment is made.
FRANK JENNINGS, Group Secretary,
Southampton Group Hospital Management Committee.
Bullar-street, Southampton.

ST. ALBANS (near), HERTFORDSHIRE. SHENLEY HOSPITAL. (2360 Beds.) Applications are invited for the post of JUNIOR HOSPITAL MEDICAL OFFICER (psychiatry) which offers experience in all branches of psychiatry, including modern forms of treatment. Single accommodation available. The Hospital is 15 miles from London, and may be visited by appointment.

Application forms obtainable from, and returnable to, the Group Secretary by 2nd September.

ST. HELENS AND DISTRICT HOSPITAL MANAGEMENT COMMITTEE. ST. HELENS HOSPITAL. (196 Beds.) Applications are invited for the post of RESIDENT HOUSE SURGEON, which becomes vacant from 1st September, 1957. The post is recognised for Pre-registration Service and for the F.R.C.S. examination.

Applications, stating age, date of qualification, and experience, and giving 2 names for reference, should be forwarded to N. RICHARDS, Group Secretary, Whiston Hospital, Prescot, Lancs, immediately.

STOCKPORT. CHERRY TREE HOSPITAL. (Isolation —96 Beds.) Applications are invited for the post of SENIOR HOUSE OFFICER.

Applications, stating age, experience, and qualifications, together with copies of 2 testimonials, to be addressed to the Secretary, Stockport and Buxton Hospital Management Committee, 59B, Shaw-heath, Stockport.

STOCKPORT AND BUXTON HOSPITAL MANAGEMENT COMMITTEE. Applications are invited for the following posts, which are approved for pre-registration purposes.

Stockport Infirmary (163 Beds)

HOUSE OFFICER (general surgery and gynæcology). Recognised for the F.R.C.S. Vacant 21st August, 1957.

HOUSE OFFICER (general surgery and ophthalmology). Recognised for the F.R.C.S. and D.O.M.S. Vacant 11th September, 1957.

Applications, with copies of 2 testimonials, to the Group Secretary, 59B, Shaw-heath, Stockport.

STOKE-ON-TRENT. CITY GENERAL HOSPITAL. HOUSE OFFICER (obstetrics and gynæcology) required, vacant shortly. Pre-registration post. Recognised for M.R.C.O.G. and D.Obst.R.C.O.G.

Applications to Hospital Management Committee Secretary, Princes-road, Stoke-on-Trent, as soon as possible.

STOKE-ON-TRENT. CITY GENERAL HOSPITAL. (815 Beds.) HOUSE OFFICER (general surgery) required, vacant end August. Pre-registration post. Hospital recognised for F.R.C.S.

Detailed applications, with copy testimonials, to Group Secretary, Hospital Management Committee, Princes-road, Stoke-on-Trent.

STOKE-ON-TRENT. CITY GENERAL HOSPITAL. HOUSE OFFICER (pædiatrics) required, vacant very shortly. Pre-registration post.

Detailed applications, with copy testimonials, to Group Secretary, Princes-road, Stoke-on-Trent.

STOKE-ON-TRENT. NORTH STAFFORDSHIRE ROYAL INFIRMARY. (455 Beds.) HOUSE OFFICER (general surgery) required. Pre-registration post. Hospital recognised for F.R.C.S.

Detailed applications, with copy testimonials, to Group Secretary, Hospital Management Committee, Princes-road, Stoke-on-Trent.

SWANSEA. MORRISTON HOSPITAL. (501 Beds.) GLANTAWE HOSPITAL MANAGEMENT COMMITTEE. Applications are invited for the post of SENIOR HOUSE OFFICER in the Department of Neurosurgery at the above Hospital. The Department is the centre for neurosurgery for South West Wales and the post offers facilities for the study of neurology for those studying for higher qualifications.

Applications, together with copies of 2 recent testimonials, should be forwarded to the Medical Superintendent of the Hospital. T. E. JONES, Group Secretary.

TAPLOW, near MAIDENHEAD. CANADIAN RED CROSS MEMORIAL HOSPITAL. HOUSE PHYSICIAN required for post vacant 14th September. Pre-registration post.

Applications, stating age, experience and qualifications with dates, with copies of 2 testimonials, to Secretary.

TAPLOW, near MAIDENHEAD. CANADIAN RED CROSS MEMORIAL HOSPITAL. Locum OBSTETRIC AND GYNÆCOLOGICAL REGISTRAR required 26th August–8th September.

Applications, with copies of 2 recent testimonials, to Secretary.

TAPLOW, near MAIDENHEAD. CANADIAN RED CROSS MEMORIAL HOSPITAL. SENIOR HOUSE OFFICER (anæsthetics) required. Post which is tenable for 1 year will be resident.

Applications, with names of 2 referees, to Secretary.

SWINDON AND DISTRICT HOSPITAL MANAGEMENT COMMITTEE. Applications invited for the appointment of SENIOR HOUSE OFFICER as Casualty Officer and Orthopædic House Surgeon at Great Western Hospital, Swindon. Post recognised by R.C.S. for 6 months of years training under Fellowship regulations. Work of Accident and Orthopædic Department, associated with Nuffield Orthopædic Centre (Wingfield Morris Orthopædic Hospital), Oxford, includes large number of industrial injuries. Salary £819 10s. p.a., less charge for residential emoluments.

Full details and names of 3 referees to Secretary, 7, Okus-road, Swindon, Wilts, immediately.

TAUNTON AND SOMERSET HOSPITAL. Applications are invited for the post of SENIOR HOUSE OFFICER (casualty and orthopædic), vacant now.

Applications, stating age, nationality and qualifications together with the names of 2 referees, should be forwarded to the Group Secretary, Taunton Hospital Management Committee, Taunton and Somerset Hospital, Musgrove Park Branch, Taunton, Somerset.

TORQUAY. TORBAY HOSPITAL. Resident Senior HOUSE OFFICER (surgery) required mid-September, 1957. Post recognised for F.R.C.S. There is a complement of 6 Resident House Officers.

Applications, stating qualifications, age, nationality, with copy testimonials (quoting Ref. F.955/83), to the Group Secretary, Torquay District Hospital Management Committee, Torbay Hospital, Torquay, S. Devon.

WAKEFIELD. PINDERFIELDS GENERAL HOSPITAL. SENIOR HOUSE OFFICER required for the Orthopædic Department. Salary £819 10s. p.a., £150 p.a. charged for accommodation.

Address written applications, giving full particulars of experience and 2 names and addresses for reference, to—

W. BOWRING, Group Secretary.

Pinderfields General Hospital, Wakefield.

WAKEFIELD. PINDERFIELDS GENERAL HOSPITAL. Applications invited from registered medical practitioners for post of JUNIOR HOSPITAL MEDICAL OFFICER in Anæsthetics (recognised for D.A. and F.F.A.R.C.S.). The post offers wide experience, as large Orthopædic and Thoracic Units are located in the Hospital in addition to the general surgical and gynæcological wards. Appointment may be either resident or non-resident. If resident, a charge at the rate of £170 p.a. will be made.

Address written applications, stating age, nationality, qualifications with dates, experience, details of previous appointments, and 2 names and addresses for reference, to—

W. BOWRING, Group Secretary.

Pinderfields General Hospital, Wakefield.

WARRINGTON GENERAL HOSPITAL. (344 Beds.) Applications are invited for the post of SENIOR HOUSE OFFICER (pædiatrics), Male or Female. Post recognised for D.C.H. The post will become vacant on 1st October, 1957. Scale of salary £819 10s. p.a., less a deduction of £150 p.a. for residential emoluments.

Applications to be forwarded to—

HENRY L. BOOT, Group Secretary,

Warrington and District Hospital Management Committee.

c/o General Hospital, Warrington, Lancs.

WATFORD AND DISTRICT PEACE MEMORIAL HOSPITAL. NORTH WEST METROPOLITAN REGIONAL HOSPITAL BOARD. REGISTRAR in Radiology required for the above Hospital. Post recognised for the D.M.R.D. Hospital may be visited by direct appointment. Post vacant immediately.

Application form obtainable from, and returnable to, the Secretary, West Herts Group Hospital Management Committee, 9, Rickmansworth-road, Watford, Herts, by not later than 10 days after appearance of this advertisement.

WATFORD, HERTFORDSHIRE. PEACE MEMORIAL HOSPITAL. CASUALTY OFFICER (Senior House Officer). Modern Department employing 3 full-time Casualty Officers. Post recognised for F.R.C.S. Resident or non-resident. Vacant immediately.

Applications, with names of 2 referees, to the Administrator.

WEST DORSET GROUP HOSPITAL MANAGEMENT COMMITTEE. Applications are invited for 2 resident 6-monthly posts of HOUSE PHYSICIAN at :—

(*a*) WEYMOUTH AND DISTRICT HOSPITAL (124 Beds), vacant mid-September.

(*b*) DORSET COUNTY HOSPITAL, DORCHESTER (109 Beds), vacant 1st October.

Both posts are approved for Pre-registration Service.

Applications, stating age, qualifications, experience and nationality, together with copies of testimonials, to the Group Secretary, West Dorset Hospital Management Committee, Damers-road, Dorchester, Dorset, immediately.

WIGAN AND LEIGH HOSPITAL MANAGEMENT COMMITTEE.

Royal Albert Edward Infirmary, Wigan

HOUSE SURGEON.

Leigh Infirmary

HOUSE SURGEON.

Both pre-registration posts—becoming vacant shortly.

Applications, with names of 2 referees, to the Secretary, Knowsley House, Wigan.

WINCHESTER. ROYAL HAMPSHIRE COUNTY HOSPITAL. (315 Beds.) HOUSE SURGEON (post recognised by Royal College of Surgeons) required for general surgery with some E.N.T. duties. Approved pre-registration post. Vacant 28th August.

Applications, with copies of 2 testimonials, to Group Secretary.

WOODFORD BRIDGE, WOODFORD GREEN, ESSEX. CLAYBURY HOSPITAL (for nervous and mental disorders). Applications are invited for the post of Full-time SENIOR HOUSE OFFICER (resident or non-resident). Board-residence for an unmarried applicant for which a charge of £150 p.a. will be made, is available. The Hospital has over 2000 Beds and an admission-rate of over 1300 each year. All forms of treatment are undertaken and outpatients clinics at general hospitals are run by the Hospital staff. Clinical conferences and seminars for the D.P.M. candidates are held weekly and facilities will be offered to attend lectures in London (1 hour's journey). Previous general but not psychiatric experience necessary.

Applications, with full particulars and names and addresses of 2 referees to be sent to the Physician-Superintendent not later than 7 days after the appearance of this advertisement.

WOKINGHAM. PINEWOOD HOSPITAL. (230 Beds with a Thoracic Surgical Unit.) MEDICAL REGISTRAR required at above Hospital. Bronchitis Unit and beds for non-tuberculous conditions of the chest. Unfurnished flat available ; residential quarters for single man or woman also available.

Application forms from, and returnable to, Secretary, Windsor Hospital Management Committee, Alma-road, Windsor, by 24th August.

WOLVERHAMPTON. NEW CROSS HOSPITAL. (634 Beds.) Pre-registration HOUSE OFFICER in General Surgery. Vacant early September.

Applications to the Hospital Secretary.

WOLVERHAMPTON GROUP. New Cross Hospital. RESIDENT JUNIOR HOSPITAL MEDICAL OFFICER required. Geriatric Department of 260 Beds. Consultant Geriatrician recently appointed and active inpatient treatment and outpatient clinics are being started.

Applications to Group Secretary, The Royal Hospital, Wolverhampton.

WORCESTER ROYAL INFIRMARY. (213 Beds.) House PHYSICIAN required end of September for Pædiatric Department, which is a busy modern unit of 26 Beds. Post recognised for D.C.H.

Applications to Hospital Secretary.

WORKSOP. VICTORIA HOSPITAL. (122 Beds.) SHEFFIELD REGIONAL HOSPITAL BOARD. Whole-time RESIDENT REGISTRAR (orthopædics and casualty) required immediately. Appointment for 1 year in first instance.

Apply to Secretary, Sheffield Regional Hospital Board, Old Fulwood-road, Sheffield, by 26th August, 1957, giving age, nationality, qualifications, present and previous appointments with dates, naming 3 referees.

DUBLIN. SIR PATRICK DUN'S HOSPITAL. Whole-time SURGICAL REGISTRAR AND SURGICAL TUTOR (combined post) required. Salary range £850–£1050.

Applications, together with copies of testimonials and names of 2 referees, should reach the Registrar of the Hospital not later than 20th September, 1957.

NORTHERN IRELAND HOSPITALS AUTHORITY. Applications are invited for a whole-time post as REGISTRAR in Neurology at hospitals managed by the Belfast Hospital Management Committee. The terms and conditions will be in accordance with the application of the Spens report to Northern Ireland.

Applications to be made on a form obtainable (with further particulars) from the Secretary, Northern Ireland Hospitals Authority, 44/46, Queen-street, Belfast, and to be returned not later than 31st August, 1957.

IBADAN, NIGERIA. UNIVERSITY COLLEGE HOSPITAL. CHILDREN'S DEPARTMENT. The Board of Management invite applications from medical practitioners with the requisite postgraduate experience and qualifications for the posts of REGISTRARS in the newly completed Hospital.

The salary offered for these posts is £1164 p.a. rising to £1212 p.a. in the second year, plus an inducement allowance, payable to an expatriate doctor, of £270 p.a.

It is hoped that 3 wards containing in all 72 Beds and a Premature Baby Unit of 15 Cots will be fully opened before the end of the year.

The teaching of undergraduate students will start in October, 1957.

There is ample scope for research work and the unit has a well-equipped research laboratory, but as yet no laboratory technician.

The appointments will be initially for 1 tour of 12 months and will be renewable by mutual agreement for a further tour of 12 months.

On satisfactory completion of the agreement a gratuity of £37 10s. will be paid for each completed term of 3 months service.

An outfit allowance of £60 is payable on first appointment. Partly furnished quarters are provided at a rental of 8½% of salary, and the Officer appointed will be eligible for 7 days leave in the United Kingdom on full pay for each completed month of service in Nigeria. Nigerian Officers taking leave in Nigeria will be entitled to 5 days leave on full pay for each completed month of service.

Free first-class passages are provided for expatriate doctors and their wives on first appointment and on completion of their agreement. Free first-class passages to Nigeria will, in certain circumstances, be provided for non-expatriate doctors. Free first-class passages will be provided on vacation leave.

Candidates will be eligible for children's allowance in accordance with current regulations.

Arrangements can be made to enable doctors to continue their National Health Service superannuation scheme contributions, and details of the revised salary and gratuity in such cases will accompany application forms.

Applications should be submitted not later than 31st August, 1957, on the appropriate forms, which will be forwarded together with additional information, on receipt of an addressed foolscap envelope, by the Adviser on Staff Recruitment (London Office, University College Hospital, Ibadan), 57, Catherine-place, London, S.W.1.

IBADAN, NIGERIA. UNIVERSITY COLLEGE HOSPITAL. The Board of Management invite applications from experienced medical practitioners for the appointment of REGISTRAR (Department of Pathology) in the newly completed Hospital.

The salary offered for the post is : first year £1164 p.a. ; second year £1212 p.a.

An inducement allowance is payable to expatriate officers of £270 p.a. The appointment will be initially for 1 tour of 12 months and will be renewable by mutual agreement for a further tour.

On satisfactory completion of the agreement a gratuity of £37 10s. will be paid for each completed period of 3 months service.

An outfit allowance of £60 is payable on first appointment. Partly furnished quarters are provided at a rental of 8½% of salary, and the Officer appointed will be eligible for 7 days leave in the United Kingdom on full pay for each completed month of service in Nigeria. Nigerian Officers taking leave in Nigeria will be entitled to 5 days leave on full pay for each completed month of service.

Free first-class passages to and from Nigeria are provided for an expatriate doctor and his wife on first appointment, vacation leave and on completion of agreement. Free first-class passages to Nigeria will, in certain circumstances, be provided for non-expatriate doctor.

Candidates will be eligible for children's allowances in accordance with existing regulations.

Arrangements can be made to enable doctors to continue their National Health Service superannuation scheme contributions, and details of the revised salary and gratuity payable in such cases will accompany application forms.

Applications should be submitted not later than 31st August, 1957, on the appropriate forms, which will be forwarded together with additional information, on receipt of an addressed envelope, by the Adviser on Staff Recruitment, London Office (University College Hospital, Ibadan), 57, Catherine-place, Palace-street, London, S.W.1.

CANADA. ROYAL VICTORIA HOSPITAL, Montreal, CANADA. Applications for JUNIOR INTERNSHIP and RESIDENCIES for the year beginning 1st July, 1958, from residents of the British Isles will be welcomed by the above Hospital, a teaching hospital of McGill University. Each rank carries full maintenance and the following monthly stipends : Junior Interns, $40 ; Junior Assistant Residents, $60 ; Assistant Residents, $100 ; Residents, $150.

Inquiries should be directed to the Executive Director, Dr. J. GILBERT TURNER.

U.S.A. CAMBRIDGE, MASSACHUSETTS. Applications are invited for the positions of RESIDENCIES in Anesthesia for a 2-year period beginning 1st July and 1st September, 1957. Salary $1800 first year and $3600 second year and full maintenance. Training in all branches of anesthesia: Affiliation with other hospitals.

Applications, stating age, nationality, qualifications, and experience, together with the names of their referees, should be forwarded to the Director of Anesthesiology, P.O. Box 89, Cambridge, Massachusetts. Travelling expenses to and from the U.S.A. will be paid. Particulars will be sent as soon as application is received. Please enclose recent photograph with application.

Public Appointments

BOLTON. COUNTY BOROUGH OF BOLTON. Applications are invited for the appointment of ASSISTANT MEDICAL OFFICER OF HEALTH AND SCHOOL MEDICAL OFFICER from suitably qualified registered medical practitioners (Male or Female). The post will be mainly of a clinical nature, but opportunity will be given for experience in general public health activities. The possession of a D.P.H., D.C.H., or D.Obst. R.C.O.G. is desirable but not essential. The salary scale for the post is £1050–£50(3)–£1200–£55(5)–£1475. In fixing the commencing salary consideration will be given to previous experience and to the possession of higher qualifications. The appointment will be superannuable, and the successful candidate will be required to pass a medical examination. The appointment will be terminable by 3 months notice on either side.

Applications, giving full particulars of age, qualifications, and experience, and the names and addresses of 3 persons to whom reference may be made, should be received by me not later than 7th September, 1957, quoting reference PH. 49.

Town Hall, Bolton. PHILIP S. RENNISON, Town Clerk.

DERBYSHIRE COUNTY COUNCIL. County Health DEPARTMENT. ASSISTANT MATERNITY AND CHILD WELFARE MEDICAL OFFICERS AND SCHOOL MEDICAL OFFICERS. Applications are invited from registered medical practitioners for whole-time superannuable posts. Salary £1050–£50–£1200–£55–£1475 p.a. Car allowance.

Particulars and forms of application are obtainable from Dr. J. B. S. MORGAN, County Medical Officer, St. Mary's Gate, Derby, to whom they should be returned by 26th August, 1957.

THE MEDICAL SERVICE OF THE ROYAL NAVY

VACANCIES FOR MEDICAL OFFICERS

Candidates are invited for Short Service Commissions of 3 years, on termination of which a gratuity of £600 (tax free) is payable. Ample opportunity is granted for transfer to Permanent Commissions on completion of 1 year's total service. Officers so transferred are paid instead a grant of £1500 (taxable).

All entrants are required to be British subjects whose parents are British subjects, medically qualified, physically fit, and to pass an interview.

Full particulars from the Admiralty Medical Department. Queen Anne's Mansions, St. James's Park, London, S.W.1.

HERTFORDSHIRE COUNTY COUNCIL. Assistant COUNTY MEDICAL OFFICER. Diploma in Public Health or Child Health desirable, but not essential. Salary £1050–£1475. Car necessary. Travelling and subsistence according to national scale.

Application forms and further particulars from County Medical Officer, County Hall, Hertford. Forms to be returned by 30th August.

HER MAJESTY'S OVERSEAS CIVIL SERVICE. British HONDURAS. MEDICAL OFFICERS required for general duties. Appointments on permanent basis with pension (non-contributory), or on short-term agreement, renewable if desired. Doctors from National Health Service may retain their superannuation rights up to 6 years and receive gratuity (taxable) of 20% of aggregate of their salary after engagement. Salary scale £922 10s.–£1385 a year. Private practice in district towns permitted, but in Belize an allowance of £125 a year payable in lieu. Quarters if available at rental of 7½% of salary, subject to a maximum charge of £120 a year. Main items of furniture provided at rental of 6% a year of value of each item supplied. Income-tax at local rates. Free passages on appointment for Officer, wife and children, not exceeding 5 persons in all. On leave, passages for Officer and wife, and not more than 2 children. Local leave permissible and generous home leave granted after each tour of from 2 to 3 years. Candidates must possess medical qualifications registrable in the United Kingdom.

Application forms from the Director of Recruitment, Colonial Office, Great Smith-street, London, S.W.1 (quoting No. BCD. 117/31/01).

HER MAJESTY'S OVERSEAS CIVIL SERVICE. Sierra LEONE. SPECIALIST ANÆSTHETIST required to undertake anæsthetic duties in Freetown hospitals, organise anæsthetic services in Government hospitals throughout the territory, and instruct medical officers and dressers. Candidates must possess medical qualifications registrable in the United Kingdom, and F.F.A.R.C.S.(Eng.) or equivalent.

Appointment :—

(*a*) On 3 years probation for permanent and pensionable employment with pension (non-contributory) at rate of 1/600th of the final pensionable emoluments for each completed month of reckonable service.

(*b*) From National Health Service, candidate retaining superannuation rights up to 6 years, and receiving gratuity (taxable) of 20% of aggregate of salary.

(*c*) Short-term contract (2 tours each of 18–24 months duration), with gratuity (taxable) of £37 10s. for each completed period of 3 months service, payable on satisfactory completion of appointment.

Salary under (*a*) and (*b*) £2170 a year, and under (*c*) £2352.

Only permanent officers can be members of Her Majesty's Overseas Civil Service. Quarters normally available at low rental. Return sea passages for Officer, wife and up to 2 children under 19 years of age or allowance in lieu if children are maintained outside Sierra Leone for the whole of the tour. Income-tax at local rates. Local leave permissible and generous home leave after each tour.

Application forms from Director of Recruitment, Colonial Office, London, S.W.1 (quoting No. BCD.117/15/016).

HER MAJESTY'S OVERSEAS CIVIL SERVICE. Uganda. MEDICAL OFFICERS with qualifications registrable in the United Kingdom required for general duties. Successful candidates may be posted to any station in Uganda. During earlier years of service an officer will be expected to carry out general medical and surgical duties including a varying amount of public health administration and the training of subordinate African medical staff. In most stations, even if remote from larger towns, it is possible to maintain interest in any particular branch of medicine or surgery to which the officer is attracted. In most stations the work is based on a district hospital which may vary in size from a comparatively small hospital meeting the needs of a backward community to a large hospital with modern facilities where specialisation in the different branches of medicine, surgery and obstetrics is possible. Appointments can be on permanent basis, subject to 2 years probation, with pension (non-contributory) or on 30–36 months contract with gratuity (taxable) payable on satisfactory completion of service. Normal retiring age is 55 but at age 45 officers may retire with full pension earned. Gratuity for contract service is 13½% of total salary drawn, not including allowances. Candidates from National Health Service may retain superannuation rights up to 6 years and receive gratuity (taxable) of 20% of their salary after engagements. Salary ranges from £1284 to £2115. Starting point determined by experience. 4 extra increments can be given to successful candidates possessing F.R.C.S., M.R.C.P. and D.P.H., and other approved higher qualifications. Other allowances in accordance with current regulations. Permanent Medical Officers are eligible to be considered for promotion to super-scale posts in Uganda and other territories in medical administration or, if they possess higher qualifications and suitable experience, in specialist posts. Quarters provided at rental varying from £21 to £60 according to size and type, and hard furniture at a rate of £12–£24 according to scale. Free air passages for each journey are provided up to equivalent of 4 adult tourist class air fares for Officer, wife and dependent children. If, in the interest of Government an Officer is required to proceed on leave after a short tour of 15–18 months, there is no limit to the number of family passages. Taxation at East African rates, generous home leave granted after each tour in addition to which casual leave is allowed at the rate of 16 days p.a. Primary educational facilities available in all the larger stations. Education subsidies are payable to Officers, which vary from £90 a year (or half the school fees, whichever is less), for primary education for first child, to £190 a year (or three-fifths of school fees, whichever is less) for secondary education for each of second and subsequent children.

Application forms obtainable from Director of Recruitment, Colonial Office, London, S.W.1 (quoting No. BCD.117/9/02).

HER MAJESTY'S OVERSEAS CIVIL SERVICE. Hong KONG. Male MEDICAL OFFICERS required for general duties. Appointment on 2 years probation for permanent and pensionable employment. Salary including expatriation pay £1305–£2486 5s. a year. Temporary non-pensionable, cost-of-living allowance depending on family circumstances also payable. Free passages for Officer, wife and up to 3 children under 18 years. Government quarters, with heavy furniture, normally available at low rental shortly after officer's arrival. Assistance towards hotel or hostel accommodation given until quarters available. Income-tax at local rates. Generous leave. Pension 1/600th of final pensionable emoluments for each completed month of service. Educational facilities available. Candidates must possess qualifications registrable in United Kingdom.

Application forms from Director of Recruitment, Colonial Office, London, S.W.1 (quoting No. BCD.117/51/03).

INVERNESS COUNTY COUNCIL invite applications from registered medical practitioners, preferably holding the D.P.H. or similar qualifications, for the appointment of ASSISTANT MEDICAL OFFICER. The candidate appointed will participate in all the work of the department. Experience in School Health Service and tuberculosis an advantage. Salary £1050 p.a. by 8 increments to £1475 p.a. Post is superannuable.

Applications, accompanied by a copy of 1 recent testimonial and the names of 2 referees, should be lodged with the County Clerk, County Buildings, Inverness, by 26th August, 1957.

MIDDLESEX COUNTY COUNCIL. County Health DEPARTMENT. SENIOR AIRPORT MEDICAL OFFICER required. Directly responsible to County Medical Officer for day-to-day administration of Health Control Service and to the Ministry of Civil Aviation for medical examination of air crews, treatment of accident casualties, &c., at London Airport. Will also undertake such other duties as may be required. Shift duties necessary to provide 24-hour service every day. Salary £1520–£1955 p.a., inclusive. Unestablished, subject to medical assessment. Prescribed conditions, which include vaccination against smallpox, prior to appointment, and annually thereafter.

Apply (no forms), stating age, qualifications, experience, names of 2 referees, to County Medical Officer (Ref. : 'S'), 3, 5 and 7, Old Queen-street, S.W.1, by 28th August (quote V 844 TL). Canvassing disqualifies.

WEST HARTLEPOOL. COUNTY BOROUGH OF WEST HARTLEPOOL. Applications are invited for the appointment of ASSISTANT MEDICAL OFFICER OF HEALTH from registered medical practitioners possessing the D.P.H. or D.C.H. The duties will be mainly in connection with Maternity and Child Welfare Services but the person appointed will be required to carry out such other duties (e.g., School Health Service duties) as may from time to time be allocated by the Medical Officer of Health. The appointment will be subject to the Whitley Council scale and conditions. Salary £1050 p.a.–£50–£1200–£55–£1475 p.a., according to experience. A car allowance of £75 p.a. is normally payable. The appointment will be subject to a medical examination for superannuation purposes and to 2 months notice in writing on either side. Canvassing will be a disqualification, and candidates must disclose any relationship to members of the Council.

Applications, stating the names and addresses of 3 referees, must be received by the Medical Officer of Health, Durham House, Victoria-road, West Hartlepool, not later than 31st August, 1957. ERIC J. WAGGOTT, Town Clerk.

Municipal Buildings, West Hartlepool, 12th July, 1957.

WEST HARTLEPOOL. COUNTY BOROUGH OF WEST HARTLEPOOL. Applications are invited for the appointment of DEPUTY MEDICAL OFFICER OF HEALTH AND DEPUTY PRINCIPAL SCHOOL MEDICAL OFFICER from registered medical practitioners possessing the Diploma in Public Health or similar qualifications. Candidates should have experience in the ascertainment of educationally subnormal pupils and preferably be approved by the Ministry of Education for this purpose. The officer appointed will be required to carry out such duties as shall be allocated from time to time by the Medical Officer of Health. The salary scale applicable to the post is £1396 p.a., rising by yearly increments of £52 10s. to a maximum of £1606 p.a. Previous service with a local authority will be taken into account in fixing the commencing salary within this scale. A car allowance of £75 p.a. has been paid to the present holder of the post. The appointment will be terminable by 3 months notice in writing on either side. The successful applicant will be required to pass a medical examination.

Applications, giving full details of the applicant's age, experience, and qualifications, together with names and addresses of 3 referees, should be sent to reach the Medical Officer of Health, Durham House, Victoria-road, West Hartlepool, not later than Saturday, 7th September, 1957.

ERIC J. WAGGOTT, Town Clerk.

Municipal Buildings, West Hartlepool, 7th August, 1957.

General Practice

For an ***Executive Council post*** *(England and Wales) apply on form* E.C.16A *obtainable from the council. Mark envelope "Vacancy."*

BERMUDA. Owing to sudden death, Vacancy exists in Group practice for a Consultant Surgeon with considerable experience in general surgery with higher qualifications. Age 35–45. Excellent salary offered.

Reply with (1) full particulars, (2) names of 3 referees, and (3) recent personal photograph to BERMUDA MEDICAL ASSOCIATES, c/o Bermuda Travel Information Office, 6, Lower Regent-street, London, W.1, within 10 days of advertisement appearing. Personal interviews will be conducted in London and Glasgow where full details will be available.

BIRMINGHAM, LADYWOOD. Applications invited for VACANCY (urban) due to resignation. List approximately 1800. Surgery accommodation will be available. Applications on E.C.16A to be received not later than 31st August, 1957, to—

K. F. G. DAY, Clerk of Birmingham Executive Council.

Sutton New-road, Erdington, Birmingham, 23.

Miscellaneous

British Medical Association. Applications are invited from registered medical practitioners for the post of Medical Director of the Commonwealth Medical Advisory Bureau and the International Medical Advisory Bureau of the British Medical Association at B.M.A. House in London. This post will be vacant on 1st January, 1958, but it is proposed that the successful applicant should join the Association's staff early in December in order that he may be initiated into the work of the Bureaux under the guidance of the retiring Medical Director. The post is regarded as suitable for a retired medical officer of one of the Armed Forces or of the Medical Branch of H.M. Overseas Civil Service, but other candidates are not excluded. The salary of the post is £2000 a year.

Applications, which should be accompanied by the names of 3 persons to whom reference may be made, must be received not later than 14th September, and should be addressed to the Secretary, BRITISH MEDICAL ASSOCIATION, Tavistock-square, London, W.C.1, from whom further particulars of the appointment may be obtained.

British Pharmaceutical Company currently forming several subsidiaries in Africa, requires British Medical Practitioner aged 30/40 years, with considerable clinical experience to act in an Advisory capacity to these subsidiaries. The successful applicant will be required to reside permanently in Salisbury, Rhodesia, and to travel extensively in Africa. His duties will include arranging clinical trials, supplying medical information and advising on promotional matters. The post is a responsible one. Salary not less than £2000 p.a.—Reply to : Address, No. 319, THE LANCET Office, 7, Adam-street, Adelphi, London, W.C.2.

Kuwait Oil Company requires Medical and Dental Officers. The Company has the following additional vacancies in its Medical Department in Kuwait :—

(*a*) A Medical Officer required to undertake all ophthalmological work in the Company, and should possess a D.O. or D.O.M.S. He will also be required to do General Duties.

(*b*) Medical Officers with 3–5 years experience after registration for general duties with all categories of Company Personnel. Ability to speak Arabic is most desirable.

(*c*) A Dental Surgeon with 3–5 years experience, after registration, in hospital or dental practice. There is ample scope for orthodontics for an interested man.

Total pay including allowance in local currency will be, for post (*a*) not less than £3100 p.a. and for posts (*b*) and (*c*) not less than £2700 p.a. Higher starting rates will be paid for knowledge of Arabic or experience in excess of 5 years. The posts are pensionable, and an initial kit allowance is payable.

Write for application form giving brief details to Box V/63, c/o, 191, Gresham House, E.C.2.

Medical Officers required by Falkland Islands Dependencies Survey for tour of 18 or 30 months service in Antarctic bases. Unique opportunity for research on polar physiology. Suitable candidates will be given research training at the Division of Human Physiology, National Institute for Medical Research, London. To leave U.K. in October, 1957. Salary £625 a year. Free passages, quarters, messing and canteen stores. Liberal leave on full salary. Candidates must possess qualifications registrable in the United Kingdom.—Write to the Crown Agents, 4, Millbank, London, S.W.1. State age, name in block letters full qualifications and experience, and quote M3/44020/LD.

Stewarts and Lloyds, Limited, Corby, Northants. Applications are invited from registered medical practitioners for the post of Assistant Medical Officer at the above Steel Works. Candidates should be aged 25–28 years and have completed their National Service commitments. The post represents an ideal opportunity for a young doctor commencing a career in industrial medicine. The successful candidate would be expected to work under the general direction of the Works Medical Officer, Dr. W. E. SCOTT, to whom all applications, with details of qualifications and past experience, should be sent.

The Rank Organisation Medical Service requires a whole-time Male Doctor, to take medical charge of Pinewood Studios, The Rank Laboratories, Denham, and Olympic Laboratory, Acton. The salary will be in accordance with the British Medical Association scale for an Assistant Medical Officer or Medical Officer, according to qualifications and experience.

Further particulars from the Consulting Physician, THE RANK ORGANISATION LTD., 11, Belgrave-road, London, S.W.1.

Partnership wanted, London or Home Counties, with succession within some years. Capital available for house purchase.—Address, No. 312, THE LANCET Office, 7, Adam-street, Adelphi, London, W.C.2.

The British Journal of Medical Hypnotism. Quarterly, £1 1s. p.a.—Orders to the publishers, 4, Victoria-terrace, Hove, 3, Sussex.

Applicants for posts requiring testimonials copied or duplicated should communicate with MANTON SECRETARIAL SERVICE LTD., 98, Victoria-street, S.W.1 (Phone : VICtoria 0141), who are specialists in this kind of work.

Typewriting and Duplicating. First-class work at moder-ate prices by experienced medical typists. Electric machines. —SYBIL RANG, 21, Heath-street, Hampstead, London, N.W.3 (HAM 5329/0504).

Microscopes. Highest prices paid for good modern types. Send or bring your equipment for valuation.—WALLACE HEATON LTD., 127, New Bond-street, W.1.

PUBLISHED by the PROPRIETORS, THE LANCET LIMITED, 7, Adam Street, Adelphi, in the County of London.
Printed by HAZELL, WATSON & VINEY, LTD., London and Aylesbury—Saturday, August 17, 1957.
PRINTED IN GREAT BRITAIN—Entered as Second Class at the New York, U.S.A., Office.

The new oral antibiotic therapy for common infections

Combines the dramatic new antibiotic 'CATHOMYCIN' with Penicillin G, the most widely used antibiotic ever developed; this alliance achieves the added advantages of both, while eliminating gaps in coverage presented by either antibiotic alone

'CATHOPEN' TRADE MARK

Sodium Novobiocin with Penicillin

'Cathopen' Tablets are indicated for the **immediate treatment of a wide range of common infections** which in the past have frequently been treated with Penicillin alone, often with poor results.

Some important infections where 'Cathopen' is indicated

Tonsillitis
Pneumonia
Acute otitis media
Breast abscess
Vincent's angina
Furuncles
Recurrent and persistent carbuncles
Bronchitis
Cervical lymphadenitis
Osteomyelitis
Erysipelas
Infected wounds
Staphylococcal septicaemia and enteritis
Whitlows and paronychiae
Cellulitis
Urethritis

'Cathopen' is easy to administer

ADULTS: Two tablets q.i.d. **CHILDREN:** According to body weight; e.g., 50 lbs., one tablet q.i.d.

Packings: Bottles of 16 (Basic N.H.S. price 26/8d) and in dispensing bottles of 100.
Each Tablet contains: 'Cathomycin' (as Sodium Novobiocin), 125 mg.; Potassium Penicillin G, 125,000 units.

Literature will gladly be supplied on request

MERCK SHARP & DOHME LIMITED, HODDESDON, HERTS. MSD

ACHROMYCIN* V

TETRACYCLINE BUFFERED WITH SODIUM METAPHOSPHATE

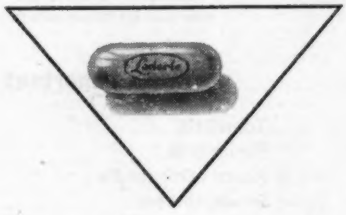
*Regd. Trademark

makes the therapy more secure

ACHROMYCIN V is an improved, oral form of ACHROMYCIN tetracycline—already recognised as today's foremost self-sufficient broad spectrum antibiotic. ACHROMYCIN V combines ACHROMYCIN tetracycline with sodium metaphosphate to provide more rapid absorption of tetracycline and higher levels of the antibiotic in the blood. This is achieved without any increase in the daily dosage of the antibiotic.

ACHROMYCIN V is presented in oral capsules containing 250 mg. ACHROMYCIN tetracycline and 380 mg. Sodium Metaphosphate.

Bottles of 16, 100 and 1000 Capsules



RECOMMENDED DOSAGE : As for ACHROMYCIN 1 Gm. daily for the average adult

CYANAMID 1907 50 1957

LEDERLE LABORATORIES DIVISION

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